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Original Communications

INTERMITTENT CLAUDICATION AS A RESULT OF ARTERIAL SPASM INDUCED BY WALKING

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THE syndrome of intermittent claudication as a result of arterial spasm alone has been regarded as unlikely by most students of the peripheral circulation. With two exceptions, the existence of such a syndrome has been ignored almost entirely in textbooks on vascular diseases and other medical writings. In 1922, Thomas,[1] a Frenchman, wrote that a brief period of arterial spasm after muscular exercise was noted in some cases in which the circulation was otherwise normal and that this spasm was followed immediately by vascular dilatation. Pearl,[2] in 1937, reported six cases in which there were symptoms of arterial insufficiency caused by arterial spasm. In his cases, the onset of pain was definitely associated with acute ischemia of the feet and diminution or disappearance of pulsations in the arteries of the feet as a result of exercise. Relief of pain coincided with return of normal color of the skin and pulsations of the arteries. In all of the cases reported by Pearl, normal or nearly normal vasodilatation occurred as a result of anesthetization of peripheral nerves. There have been reports of other cases of intermittent claudication, with a normal vasodilatation response and normal pulsations in the peripheral arteries, but the authors fail to state whether or not pulsations in the arteries disappeared as a result of walking.[3, 4] Veal[5] has shown by arteriographic studies that intermittent claudication may affect patients whose large arteries are patent throughout their course and have normal lumens. He felt that the defect in the circulation which caused intermittent claudication was in the small arterial branches, which were few in number, irregularly distributed, and considerably shorter than normal. We have ordinarily

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considered this the explanation for the intermittent claudication which affects patients whose circulation seemed normal during rest.[5] The syndrome of intermittent claudication as a result of arterial spasm induced by exercise is unusual, for almost invariably exercise causes arterial dilatation instead of spasm.[6-8]

In the past year we have observed four patients who had this syndrome.

REPORT OF CASES

CASE 1.—A man, aged 44 years, first registered at the Clinic in 1935. At that time the patient complained primarily of epigastric distress suggestive of ulcer, but he also stated that for two years prior to registration he had noted a peculiar type of muscular exhaustion in the entire left leg which was precipitated by strenuous walking and promptly relieved by resting. Examination did not disclose evidence of neurologic disease, and the arteries of the lower extremities pulsated normally. Because of the mild character of the symptoms, further investigations were not made.

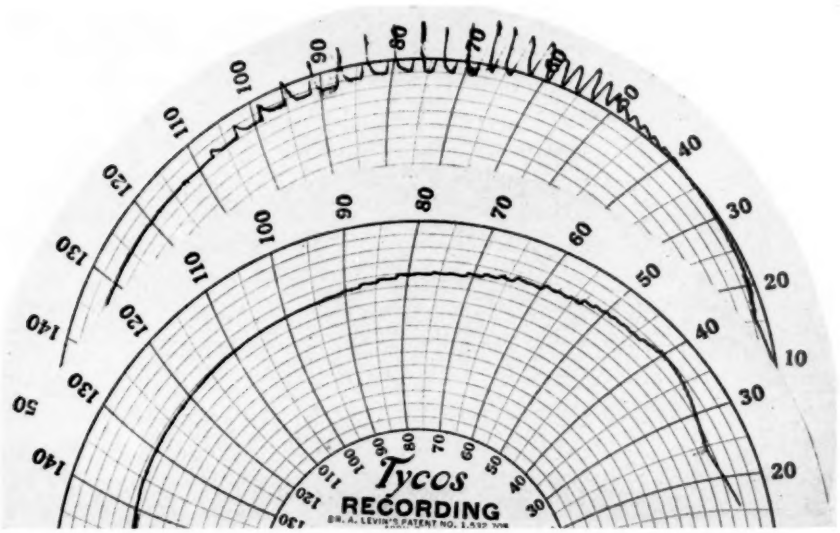

Fig. 1.—Case 1. Oscillometric records taken above the ankle; *upper record*, normal arterial pulsations when the patient was at rest; *lower record*, almost complete absence of arterial pulsations forty-five seconds after cessation of exercise.

The patient returned to the Clinic in 1939; he complained primarily of weakness which involved both legs and the trunk caudad to the level of the third lumbar vertebra. The weakness was present only after walking approximately 100 yards (91 meters) and was so severe that he was forced to stop for about a minute; the weakness then would disappear completely. By slowing his pace, he was able to walk indefinitely.

General physical examination disclosed nothing abnormal, with the exception of the peripheral circulation. The pulsations of the dorsalis pedis and posterior tibial arteries were normal when the patient was at rest. After exercise, pulsations in these arteries disappeared entirely, but reappeared about a minute after cessation of exercise. When the patient was at rest, a systolic murmur was audible over the

lower portion of the abdomen; its maximal intensity was at the midline just below the umbilicus, and its maximal transmission was to the femoral arteries. After exercise, a thrill was palpable over these arteries. The results of oscillometric studies made just below the knees confirmed the clinical observations (Figs. 1 and 2). Pulsations disappeared entirely after the patient walked up and down stairs rapidly for a minute; the return of pulsations corresponded roughly to the disappearance of symptoms. Surprisingly, the weakness of which he complained did not result from the exercise. Laboratory examination was essentially negative.

As a result of an intravenous injection of 25,000,000 killed typhoid bacilli, the temperature of the skin of the toes of the right and left feet increased from 25.2 to 34° C., and from 25.4 to 34.2° C., respectively. We consider that these increases in the temperature of skin as a result of fever induced by typhoid vaccine indicate a normal arterial circulation. When the patient still had fever and the temperature of the skin of the first toes was maximal, exercise induced arterial spasm.

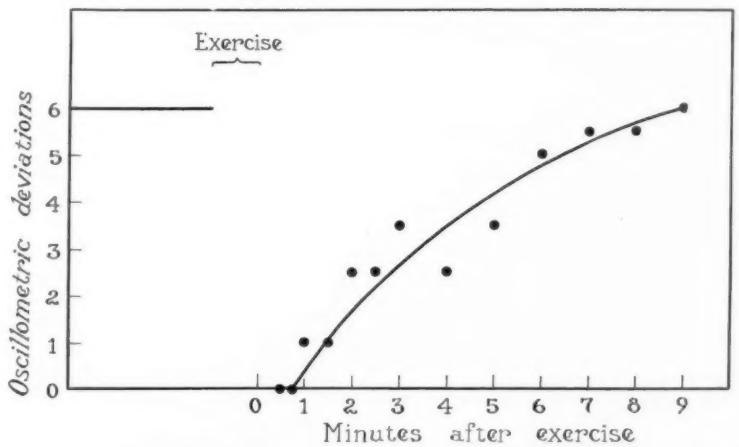

Fig. 2.—Case 1. Oscillometric deviations, taken above the ankle, of 6 units before exercise indicate normal arterial pulsations, and complete absence of oscillations immediately after exercise indicate absence of arterial pulsations. The pulsations, however, gradually returned to normal eight minutes after cessation of exercise.

The patient returned to the Clinic in April, 1940. He stated that since his last examination he had had rather severe and constant lumbar backache; two attacks of severe pain had occurred suddenly in the lumbosacral region; this pain had been crampy in character and so severe that he had gone to bed. The first attack had lasted an hour, and the second one, ten days.

Results of general physical examination were negative except for the circulation in the legs. Calcification of the abdominal aorta was evident roentgenologically. Pulsations were normal in the radial and ulnar arteries, moderately diminished in both femoral and the left popliteal arteries, greatly diminished in both posterior tibial and left dorsalis pedis arteries, and absent in the right popliteal and dorsalis pedis arteries. A systolic bruit was audible over the abdominal aorta.

A tentative diagnosis of dissecting aneurysm of the abdominal aorta was made.[9] That such a condition might be present was suggested by the systolic murmur over the aorta in the lower portion of the abdomen, by the two attacks of severe pain, by occlusion of arteries of the legs which had not been occluded at the time of the first examination of the patient, and by the roentgenologic evidence of sclerosis of the abdominal aorta which was noted after the second examination. The presence or absence of dissecting aneurysm could be determined, of course, only

at necropsy. Whatever the etiology of the spasm of the arteries of the lower extremities, the spasm unquestionably caused the syndrome of intermittent claudication.

CASE 2.—A Jewish man, aged 32 years, was examined at the Clinic in January, 1940. The patient had had swelling of both legs during the five years prior to registration. This was the result of thrombosis of the inferior vena cava, which had occurred in the course of convalescence from pneumonia. In addition, intermittent claudication had been present in the right calf for five years and in the left calf for two years. Walking 100 to 500 yards (91 to 462 meters) produced the distress, and rest relieved it in about a minute. It never occurred during rest or standing.

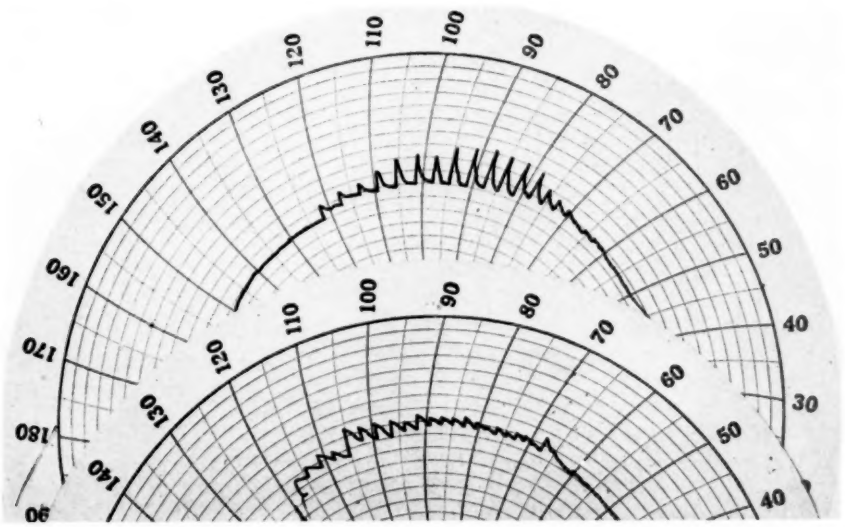

Fig. 3.—Case 2. Oscillometric records taken above the ankle; *upper record,* normal arterial pulsations when the patient was at rest; *lower record,* almost complete absence of arterial pulsations about one minute after cessation of exercise.

On physical examination, an extensive collateral venous circulation that involved both lower extremities, the abdomen, and the thorax to a level 2 inches (5 cm.) above the nipple line was noted. The arteries of the lower extremities pulsated normally except that pulsations could not be felt in either dorsalis pedis artery. As a result of walking rapidly for about a minute, pulsations in the posterior tibial arteries disappeared, but returned to normal after about four minutes of rest. The results of routine laboratory study were negative except for serologic tests for syphilis, which were equivocal and were not regarded as significant. Roentgenologic examination of the thorax disclosed nothing abnormal.

The results of oscillometric studies made just above the ankles confirmed the clinical observation of diminished arterial pulsations as a result of walking (Fig. 3). Walking caused the normal increase in pulsations in the region of the calf of the leg. Intramuscular injections of a complex pancreatic preparation (padutin) and the oral administration of alcohol, alone or in combination with the application of a rubber bandage to the legs, were found to increase the distance the patient could walk before claudication occurred. The use of the rubber bandage alone had an opposite effect. The claudication was invariably accompanied by a definite absence of pulsation in the posterior tibial arteries, as ascertained by

palpation. Decreased oscillations were also invariably associated with the intermittent claudication, and, as the symptoms disappeared with rest, the pulsations were found to return to normal.

CASE 3.—A man, aged 32 years, registered at the Clinic in January, 1940. The patient complained chiefly of chronic venous insufficiency which resulted from thrombophlebitis of the right leg after an appendectomy in 1931. He also complained of cramping distress of the right calf, which occurred after walking four or five blocks or on prolonged standing. The distress was relieved by resting for ten minutes and could be prevented by wearing a tight bandage on the calf. The distress was not characteristic of intermittent claudication; indeed, it seemed more probable that it was caused by the chronic venous insufficiency. However, if the patient walked, the pulsations in the right dorsalis pedis and posterior tibial arteries disappeared and could not be felt for about a minute after cessation of exercise, whereas pulsations in the same arteries in the left leg were unchanged as a result of walking.

CASE 4.—A man, aged 60 years, registered at the Clinic in March, 1940. For fifteen years he had had rather mild, low back pain, with extension to both hips. Two years prior to examination the pain had become sharp and rather severe and had begun in both gluteal regions, with extension upward to the lumbar region and to both hips and thighs. The distress, which was associated with a pulling sensation in both calves, was produced only by walking and was relieved almost immediately on stopping. The results of general physical examination were negative except for abnormalities relative to the arteries of the legs. When the patient was at rest, all of the arteries pulsated normally. After walking, which produced pain, the skin of the left foot became pale and the veins collapsed. The right foot remained normal in these respects. When the feet were elevated, there was moderate pallor of the skin of the left foot, and, when the feet were dependent, normal color returned slowly to the left foot. A soft, blowing, systolic bruit was audible over the abdomen 2 to 3 cm. below the umbilicus. This bruit was well localized during rest, but after exercise it was transmitted to both femoral regions.

Routine laboratory examinations of the blood and urine revealed no abnormalities. The lipoids in the blood, in milligrams per 100 c.c. of whole blood, were as follows: cholesterol, 235; cholesterol esters, 146; lecithin, 225; fatty acids, 376; and total lipoids, 611. Roentgenologic examination of the thorax revealed nothing abnormal; roentgenologic examination of the lumbar portion of the spinal column revealed hypertrophic changes and calcification of the abdominal aorta. When the patient rested in a room in which the temperature was 32.2° C., the temperature of the skin of the first and third toes of the right foot increased to 35° C. and 34.4° C., respectively, and the temperatures of the first and third toes of the left foot were 33.9° C. and 33.2° C., respectively. These studies indicated impaired circulation to the left foot. The results of examination with the oscillometer were normal for the right leg, both at rest and after exercise. Pulsations in the left calf were definitely diminished in periods of rest and after exercise were absent for approximately a minute.

COMMENT

We feel that the distress of these four patients was the result of diminished blood flow to the extremities. The diminution of blood flow definitely resulted from spasm of arteries, but we cannot explain why spasm occurred, for the usual arterial response to exercise is arterial dilation. However, systolic bruits were heard over the abdominal aortas

in Cases 1 and 4. Since the discovery of the bruit in Case 1, one of us (Leary) has examined routinely all patients for its presence, with entirely negative results. It seems to us, therefore, that such bruits indicate the presence of arterial disease. Roentgenograms of the abdominal aortas of these two patients revealed calcification. The similarity of the murmurs in Cases 1 and 4 to those produced by proved aneurysms was striking and caused us to suspect that such a lesion existed in each case. Since an aneurysm may cause interference with peripheral blood flow, it may be concluded that the circulatory disturbance observed in these cases was caused by an aneurysm, but just how such a disturbance is provoked remains unexplained.

The other two patients had had thrombophlebitis, and, at the time of examination at the Clinic, had chronic venous insufficiency. It occurred to us that venous obstruction might cause arterial spasm during exercise, but, when we had eight normal subjects run with the venous circulation obstructed by means of a tourniquet about the thigh, the pulsations in the arteries of the foot did not decrease or disappear. Also, one of us (Leary) studied the peripheral arterial pulsations, by means of an oscillometer, of twenty-five normal subjects and of eight patients who had chronic occlusive arterial diseases, both before and after exercise. In each case the arterial pulsations remained unchanged or actually increased as a result of exercise.

Acute thrombophlebitis occasionally causes absence of arterial pulsations in the affected extremity as a result of arterial spasm provoked by phlebitis. This arterial spasm apparently results from proximity to inflammation or from extension of inflammation from a vein to an artery. Such arterial spasm is, however, transient, and, in our experience, lasts but a few hours at the most. It is probable, however, that the residue of acute thrombophlebitis produced a "reverse sensitivity" of the arteries in our two cases, so that they contracted, instead of dilated, when the patient exercised. As far as is known, this is a new observation relative to arterial spasm. The exact explanation, however, remains obscure, although the clinical facts are impressive. Intermittent claudication can occur when patients walk because the arteries to the legs contract rather than dilate. This paradoxical reaction of arteries has, in our experience, indicated some disease of the arteries or veins. Whenever a patient relates a conclusive story of intermittent claudication, the physician must not exclude occlusive arterial disease as the cause of it because the arterial pulsations are normal, but he must suspect that the symptom of intermittent claudication is due to arterial spasm induced by walking, and he must study the pulsations in the arteries, both before and after exercise. If he fails to find evidence of a paradoxical reaction of the arteries, he may then consider localized obliteration of smaller arteries, as described by Veal.

REFERENCES

1. Thomas, André: L'angiospasme provoqué dans les artérites périphériques et la claudication intermittente, Presse méd. **2:** 1049, 1922.
2. Pearl, F. L.: Angiospastic Claudication. With a Report of Six Cases, Am. J. M. Sc. **194:** 505, 1937.
3. Morton, J. J., and Scott, W. J. M.: The Quantitative Determination of Vasoconstrictor Spasm as a Basis for Therapy in Peripheral Arterial Diseases, Ann. Surg. **96:** 754, 1932.
4. Horton, B. T.: Intermittent Claudication in the Extremities With Pulsating Vessels, M. Clin. North America **14:** 783, 1930.
5. Veal, J. R.: The Pathologic Basis for Intermittent Claudication in Arteriosclerosis, Am. Heart J. **14:** 442, 1937.
6. Lewis, T.: Pain in Muscular Ischemia; Its Relation to Anginal Pain, Arch. Int. Med. **49:** 713, 1932.
7. Veal, J. R., and McFetridge, Elizabeth M.: Vascular Changes in Intermittent Claudication: With a Note on the Value of Arteriography in This Symptom Complex, Am. J. M. Sc. **192:** 113, 1936.
8. McDowall, R. J S., Malcolmson, G. E., and McWhan, I.: The Control of the Circulation of the Blood, New York, 1938, Longmans, Green & Co., 619 pp.
9. Glendy, R. E., Castleman, Benjamin, and White, P. D.: Dissecting Aneurysm of the Aorta; a Clinical and Anatomical Analysis of Nineteen Cases (Thirteen Acute) With Notes on the Differential Diagnosis, Am. Heart J. **13:** 129, 1937.

SYSTOLIC GALLOP RHYTHM

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SINCE Cŭffer and Barbillon[1] first described systolic gallop rhythm, in 1887, other investigators have dealt with it. Systolic gallop rhythm is produced when an extra sound falls between the first and the second heart sounds. As to the extrasystolic sounds, various authors have included different sounds under this designation.

Systolic gallop rhythm is divided into three classes, as follows: (1) so-called systolic gallop rhythm (Potain,[2] Wolferth and Margolies[3]), (2) systolic click, and (3) systolic pericardial knock.

Potain[2] observed systolic gallop rhythm in cases of typhoid fever, typhoidlike influenza, and arteriosclerosis with aortic atheroma. He stated that the extra sound was heard best over the aortic area, and regarded it as an arterial phenomenon caused by diminished elasticity and tonicity of the aorta. He recognized systolic gallop rhythm solely by auscultation, but Wiedemann[4] and Wolferth and Margolies[3] obtained graphic records of systolic gallop rhythm, and established proof of its existence, as designated by Potain.

According to Wolferth and Margolies,[3] there are at least two types of systolic gallop sound, exclusive of various other types of sounds which may fall between the first and the second heart sounds, namely, aortic systolic gallop rhythm and apical systolic gallop rhythm; in the former the extra sound is heard best over the aortic area, as described by Potain[2] and Pawinski,[5] and in the latter it is heard best over the apex. They stated that the extra sound in aortic systolic gallop rhythm is produced in the aorta, that is to say, it is caused by sudden checking of the distention of the aortic wall during systole or by impact of the aorta against surrounding structures at that instant. They recognized this kind of extra sound in cases of hypertensive cardiovascular disease, aortic insufficiency, and miliary tuberculosis. As to the apical systolic sound, they stated that the impact of the cardiac apical region against the chest wall may be concerned in the mechanism of its production.

The character of the systolic click is quite different from the systolic gallop sound mentioned above. It is a kind of crepitant noise of very short duration, and usually it is high pitched. Gallavardin[6] and Johnston[7] stated that the click is caused by tugging on pleuropericardial ad-

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hesions during systole, and it was called by Lian and Deparis[8] "le claquement meso-systolique pleuropericardique." This extra sound has no clinical significance and has nothing to do with organic heart diseases. According to Johnston,[7] it is of maximum intensity at or near the apex, and its loudness changes with respiration or shift of position.

As to the extra sound which produces systolic gallop rhythm, there is another type, called the pericardial knock, which has many features in common with the systolic click. Pericardial knock has been the subject of research by various authors, including Rees and Hughes,[9] Smith,[10] Munden,[11] and Lister.[12] It is a short sound, and commonly louder than the click. This sound is heard occasionally after spontaneous left-sided pneumothorax, or during the therapeutic induction of left-sided pneumothorax. It is heard best at the apex and is influenced by respiration and by position. According to Barnwell and Greene,[13] it is produced when a highly active heart whose movement is not limited or cushioned by lung tissue strikes either the chest wall or the diaphragm.

We have been recording heart sounds during the past two years, and encountered ten cases of systolic gallop rhythm of various types, as follows:

A. Three cases of systolic click (one patient had mitral disease; two had no cardiac disease).

B. Two cases of systolic pericardial knock (both patients were under observation during the induction of left-sided pneumothorax).

C. Four cases of so-called systolic gallop rhythm (one patient had aortic insufficiency; two had mediastinal tumors; and one had a patent ductus arteriosus and combined mitral disease).

D. One case of auricular systolic gallop rhythm (sinoauricular block with nodal extrasystole).

We shall here report only the cases of systolic gallop rhythm in groups C and D. In group C it was proved that the gallop rhythm was caused by a mediastinal tumor in two cases. Moreover, it was shown that there may be pulmonic systolic gallop rhythm, as well as aortic and apical systolic gallop rhythm.

METHOD

For the graphic registration of the heart sounds we employed Koizumi's[14] apparatus, which is an application of high frequency current. The apparatus consists of five components, namely, a microphone, an oscillator, a detector, an amplifier, and an oscillograph. As a microphone, the author used a round metal plate (diameter, 3 cm.), insulated by a mica plate of the same size (thickness, 1 mm.) on one side; the metal plate was connected to the grid of the oscillator. This microphone is placed over the chest on its insulated side, and fixed by adhesive tape or a bandage. The microphone acts as the fixed plate of a condenser microphone, and the oscillating chest wall, which is earthed, acts as the oscillating plate of a condenser microphone.

Thus the change in electrical capacity between the fixed metal plate and the oscillating chest wall is received and magnified.

The author[15] inserted an adequate electrical filter into the circuit and caused the apparatus to be sensitive to either higher or lower frequency sounds as desired (Fig. 1).

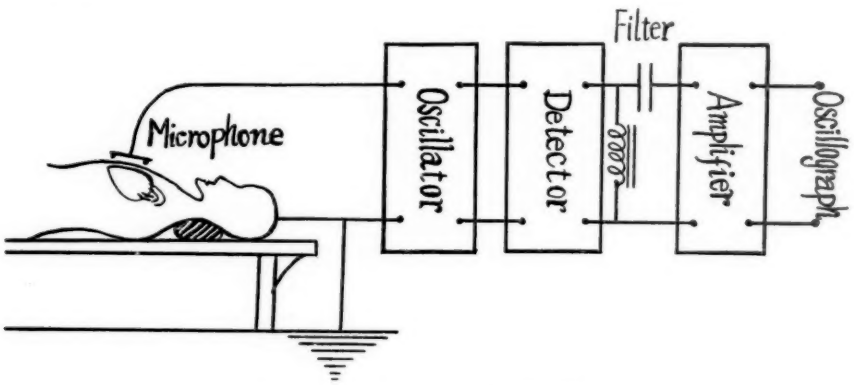


Fig. 1.—Diagram of the connection.

For recording the heart sounds through the esophagus, the following method was invented by the author.[15] For a microphone an insulated piece of metal (length, 1.5 cm.; diameter, 4 mm.) was fixed to the end of a rubber tube similar to a duodenal tube. The metal piece was connected to the grid of the oscillator of Koizumi's apparatus by a fine wire through the tube. By having the patient swallow the microphone and fixing it at a certain height we can record the oscillations of the esophageal wall as the heart sounds; the principle is the same as that of the condenser microphone mentioned above.

The heart sounds were always recorded in conjunction with Lead II of the electrocardiogram, and the time markings were at $\frac{1}{100}$ second intervals.

REPORT OF CASES

CASE 1.—R. S. was a 36-year-old woman with aortic insufficiency. She had had diphtheria at the age of 10 and rheumatic arthritis at the age of 15.

The heart was moderately enlarged to the right and left. Over the aortic area, the base, and the apex, a systolic murmur and a blowing diastolic murmur were heard. A diastolic murmur followed the second aortic sound, and was maximum in intensity over the midsternal region. Moreover, an extra sound was heard between the first and the second heart sounds over the aortic area and at the apex. A capillary pulsation was present. The blood pressure was 160/40. The electrocardiogram showed left ventricular preponderance and evidence of myocardial damage (depressed S-T segment in Lead I).

Fig. 2 shows the heart sound tracings which were recorded over the aortic area. The extra sound (*G*) fell nearly midway between the first and second heart sounds, that is to say, 0.23 second after the Q wave and 0.18 second prior to the second heart sound. The tracing indicates that it is formed by two oscillations with a frequency of 50 per second.

CASE 2.—M. I. was a 58-year-old woman with a mediastinal tumor. She complained of cough, hoarseness, and edema of the upper half of her body. These symptoms began two months before her admission.

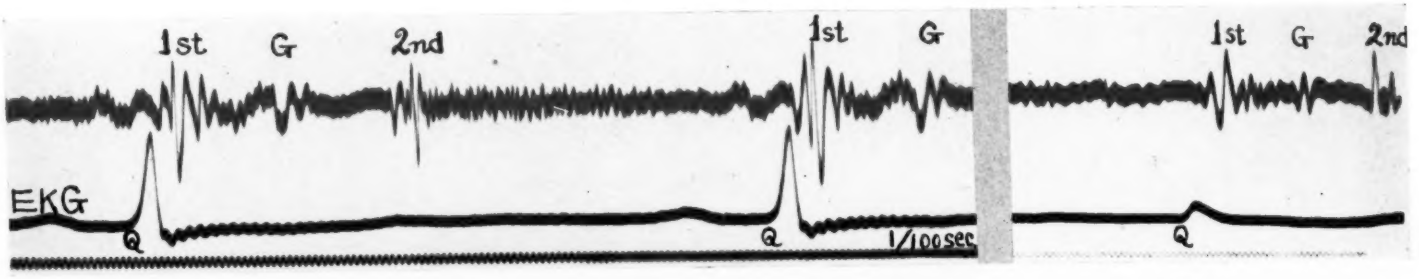
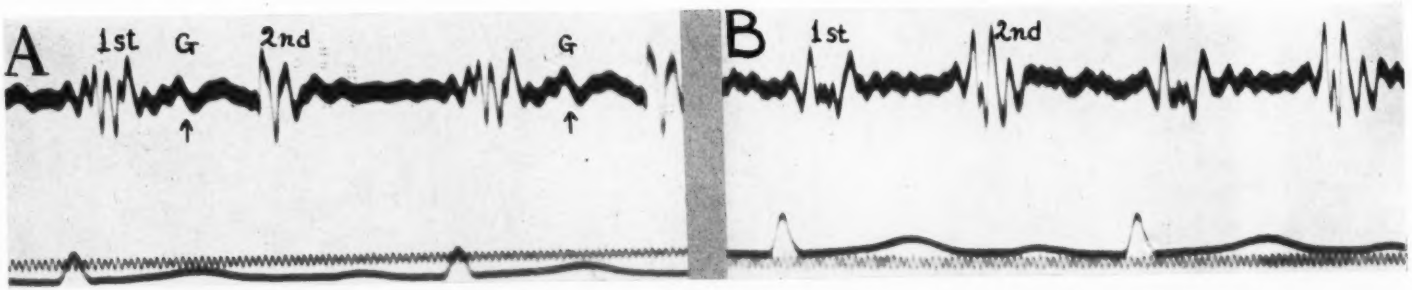


Fig. 2. Fig. 3.

Fig. 2.—Case 1. Aortic insufficiency. Systolic extra sound (*G*) is clearly shown midway between the first and second heart sounds (recorded over the aortic area).

Fig. 3.—Case 2. Mediastinal tumor. Systolic gallop rhythm is present (recorded over the aortic area).



A. *B.*

Fig. 4.—Case 3. Mediastinal tumor and pleuritis exsudativa sinistra. *A* was recorded before the withdrawal of the fluid; the systolic extra sound (inaudible), with low frequency, is recorded. *B* was recorded after the withdrawal of the fluid; no systolic gallop rhythm is shown.

Roentgenologic examination of the chest demonstrated a sharply demarcated, nonpulsatile mass in the right hilus. The heart was normal in size, and was of the dropped type. The aorta was markedly displaced to the left and upward by the mediastinal mass. The electrocardiogram showed depression of the S-T segment in Leads I and II and evidence of a drop heart. The blood pressure was 105/60. The sphygmogram revealed sclerosis of the radial artery.

Over the aortic area a soft systolic murmur and a weak, systolic, extra sound were heard. The heart sounds were recorded over the aortic area and at the apex. Systolic gallop rhythm was shown in both tracings. Referring to Fig. 3, the extra sound fell in the midsystolic phase, that is to say, 0.2 second after the Q wave and 0.11 second prior to the second heart sound. The extra sound in Fig. 2 was formed by two oscillations of a frequency of 50 to 60 per second, but the extra sound recorded over the apex was lower pitched, with a frequency of 30 to 40 per second, and it could not be recognized by auscultation.

CASE 3.—H. Y. was a 24-year-old man with a mediastinal tumor. He had had a cough for a year, which was explained by a doctor as due to a mediastinal tumor. Eleven months later it was accompanied by pleuritis exsudativa sinistra.

Physical examination prior to withdrawal of the pleural effusion showed that the apex impulse was not perceptible. The left border of cardiac dullness could not be located because of the pleural effusion on the left. The right border extended to the right margin of the sternum. The first and the second heart sounds were pure. The blood pressure was 120/60.

Physical examination after 1,000 c.c. of the pleural effusion had been removed showed that the left border of cardiac dullness was 2 cm. medial to the left nipple line, and that the right border was at the midsternal line. The first heart sound was somewhat muffled. The blood pressure was 120/40.

The electrocardiogram revealed a tendency toward right ventricular preponderance and evidence of slight myocardial damage. Roentgenologic examination of the chest showed a mass in the mediastinum which was diagnosed as a mediastinal tumor.

Heart sounds were recorded twice, that is, before (Fig. 4*A*) and after (Fig. 4*B*) removing the pleural effusion. In Fig. 4*A* an extra oscillation, with a frequency of 30 per second, is apparent between the first and second heart sound; it fell 0.18 second after the Q wave and 0.12 second prior to the second heart sound. In Fig. 4*B* no extra sound was present in the systolic phase.

CASE 4.—K. Y. was a 16-year-old girl with a patent ductus arteriosus and combined mitral failure.

The patient had complained of palpitation since her childhood. At the age of 15 years she had rheumatic arthritis. For one month previous to entering the hospital she complained of palpitation and cough and was confined to her bed.

The heart was greatly enlarged, and the apex impulse was thrusting and heaving in the sixth intercostal space 5 cm. to the left of the nipple line. The left border of cardiac dullness coincided with the apex beat. The right border of dullness was just to the right of the sternum. In the pulmonic area, that is, in the second intercostal space near the left of the sternum, abnormal dullness was recognized and pronounced thrills were felt. Over the pulmonic area a midsystolic extra sound was heard, together with a harsh systolic murmur and a weak diastolic murmur. The pulmonic second sound was accentuated. Over the apex a blowing systolic murmur, a low-pitched, rumbling, diastolic murmur, and a third heart sound were heard. Over the aortic and tricuspid areas and the base, systolic and diastolic murmurs,

decreasing in loudness, were heard. But no systolic extra sound was heard over any of the auscultatory areas except the pulmonic. When the aorta abdominalis was compressed forcibly with the hand, the pulmonic systolic murmur increased in loudness and the pulmonic second sound became more accentuated. Valsalva's test was positive.

Roentgenologic examination showed marked enlargement of the cardiac silhouette, both to the left and right, and marked prominence of the pulmonary arc (Fig. 5). The electrocardiogram revealed right ventricular preponderance and evidence of coronary insufficiency. The blood pressure was 115/30. Physical exertion caused marked elevation of the maximum pressure and depression of the minimum pressure.

Fig. 5.—Case 4. Roentgenogram taken at the time when the systolic extra sound was heard over the pulmonic area and the heart had been failing. Note the prominence of the pulmonary arc and enlargement of the heart to the left and right.

In the lung there were moist râles. The liver was enlarged. The physical signs were thought to indicate that the patient was suffering from congestive heart failure caused by patency of the ductus arteriosus and combined mitral disease.

Heart sounds were recorded over various auscultatory areas. Over the pulmonic area the systolic extra sound was conspicuous (Fig. 6). This extra sound was formed of oscillations of a frequency of 132 per second, and it fell 0.19 second after the Q wave and 0.19 second prior to the second heart sound.

The second examination was done a month later, when she had recovered from serious cardiac failure, but at this time no systolic gallop rhythm was demonstrated in the heart sound tracing. The roentgenogram revealed that the heart was slightly diminished in size, and that the pulmonary arc was not so conspicuously projected as at the first examination.

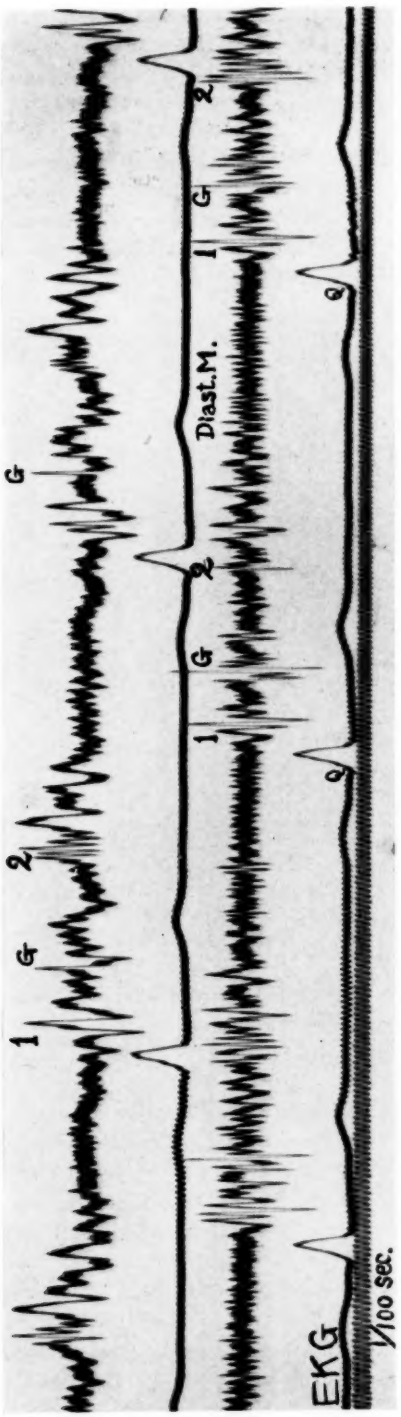


Fig. 6.—Case 4. Patent ductus arteriosus and combined mitral disease. The systolic extra sound (*G*) was present only over the pulmonic area. Upper: using no filter. Lower: using a filter. The systolic extra sound is clearly shown.

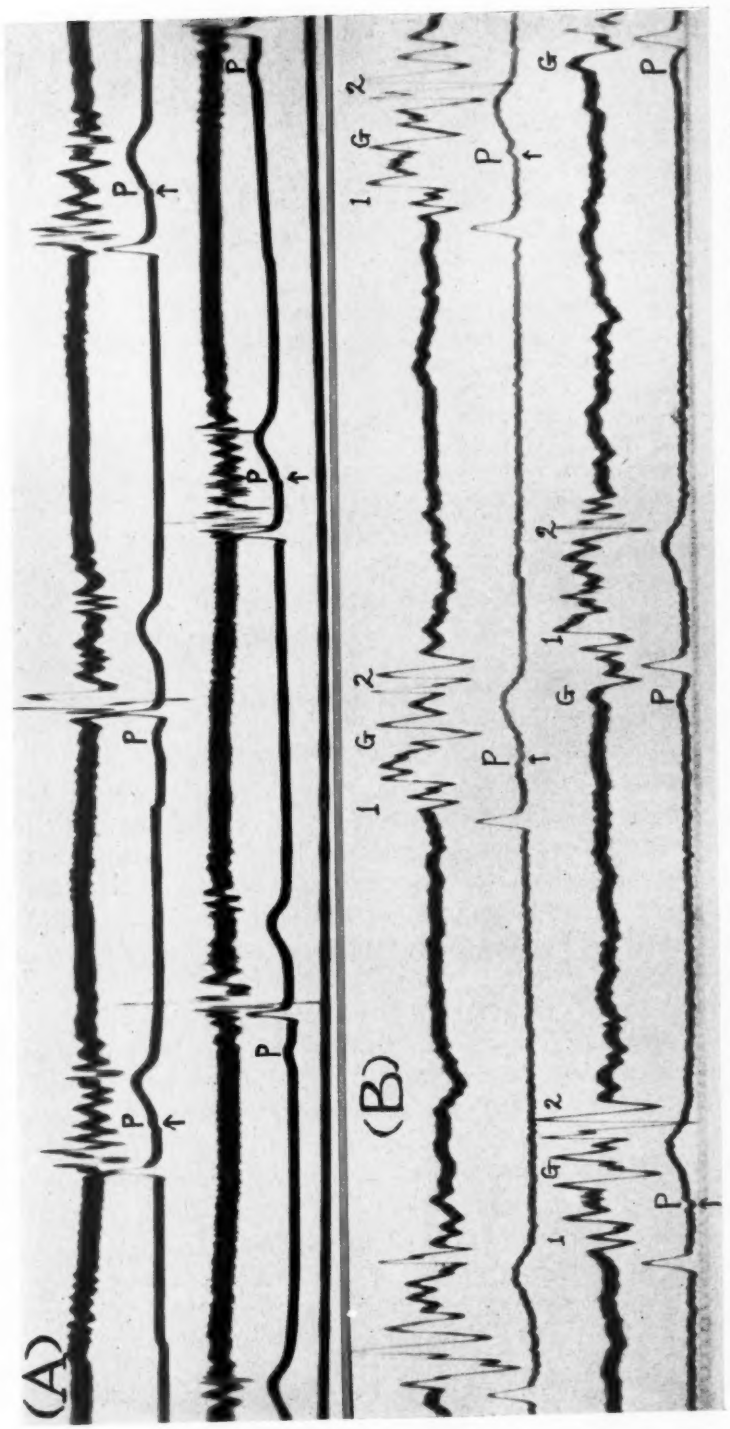


Fig. 7.—Case 5. Incomplete sinoauricular block and nodal extrasystoles. *A*: recorded over the precordium. Upper: using no filter. Lower: using a filter. The systolic extra sound (inaudible) is recognized as a mere trace on the upper strip. *B*: recorded through the esophagus at a distance of 33 cm. from the front teeth, using no filter. The sound marked as *G* is due to the auricular contraction. When the P wave of the electrocardiogram precedes the Q wave at a certain distance, the auricular sound (*G*) is heard as the presystolic gallop sound, as indicated by the last two beats in the lower strip. When the P wave, which is due to a nodal extrasystole occurs midway in the S-T segment, the auricular sound (*G*) falls between the first and the second heart sounds and systolic gallop rhythm is produced, as indicated by the second and the third beats in the upper strip and the first beat in the lower strip.

CASE 5.—Y. S. was a 36-year-old man with incomplete sinoauricular block and nodal extrasystoles. The pulse rate was 40. Except for bradycardia, he had no complaint.

The heart was normal in size and position. A moderately loud systolic murmur was heard over the apex and the base. The heart sound and murmurs varied in loudness. The electrocardiogram showed partial sinoauricular block, with nodal extrasystoles; there was evidence of myocardial damage, and the Q-T interval was prolonged to 0.49 second. The blood pressure was 140/70.

The heart sounds were recorded through the esophagus, as well as over the precordium. The esophageal heart sounds were obtained by placing the microphone in the esophagus at a distance of 33 cm. from the front teeth (Fig. 7*B*). The electrocardiogram revealed that the P wave was not uniform in its occurrence. When sinoauricular conduction was prolonged, the P wave was retarded in its occurrence and the P-Q interval was shortened. When sinoauricular conduction was blocked, the P wave appeared late in the S-T segment because of nodal extrasystoles.

Fig. 7*B* shows that the auricular sound corresponds to the P wave. When the P wave preceded the Q wave, the auricular sound was recognized as a presystolic gallop sound; whereas, when the P wave occurred late in the S-T segment, the auricular sound was recognized as a systolic gallop sound. The auricular systolic gallop sound was transmitted to the precordium also (Fig. 7*A*), but it was not so conspicuous there as in the esophagus.

DISCUSSION

We have reported five cases of systolic gallop rhythm of various types, exclusive of the systolic click and the systolic pericardial knock. Among them there were cases of gallop rhythm which was demonstrated solely in the sound tracings, and was not recognized by ascultation.

As to the genesis of systolic gallop rhythm, Potain[2] stated that it is caused by diminished elasticity and tonicity of the aortic wall. He believed that the aortic distension occurred quickly, but ceased suddenly, with tension and shock which were responsible for the sound. His theory was supported by Wolferth and Margolies,[3] who stated that systolic gallop rhythm, as described by Potain, was found in some cases of hypertensive cardiovascular disease or aortic insufficiency.

The patient in Case 1 was suffering from aortic insufficiency, and this case may be properly said to belong to the type described by Potain and Wolferth and Margolies, but in Cases 2 and 3 there was neither a valvular defect nor hypertensive cardiovascular disease. In Case 2 there may have been sclerosis of the vascular system, but in Case 3 there was no sign of arteriosclerosis. A mediastinal tumor was recognized in both cases.

Roentgenologic examination in Case 2 revealed that the aortic arc was forced markedly to the upper left part of the heart by a tumor growing in the mediastinum. We believe that in this case the extrasystolic sound was produced by the sudden checking of distention of the distorted aorta.

In Case 3 systolic gallop rhythm was recognized in the tracing, but it could not be detected by auscultation because of the low frequency

and small amplitude. This extra sound disappeared after the pleural effusion was drained. In this case, also, a mediastinal tumor was recognized in the roentgenogram. We believe that at the first examination the mediastinal tumor and pleural effusion compressed the aorta and the heart in such a way that transmission of the aortic pulsation to the precordium was facilitated, thus causing a low and weak systolic extra sound.

In Case 4 the patient had congestive heart failure. In this case the systolic extra sound was heard over the pulmonic area only, and solely during the period when the heart was extremely enlarged and decompensated. The roentgenogram which was taken at the time when the systolic extra sound was present showed marked prominence of the pulmonary arc. The extra sound occurred 0.19 second after the Q wave and seemed to correspond with the aortic extra sound. From these observations we conclude that the pulmonic systolic sound might be produced by sudden checking of the distending movement of the hypertensive pulmonary artery, or by distention of the ductus arteriosus in the midsystolic phase. Wolferth and Margolies[3] reported two types of systolic gallop rhythm, that is, aortic and apical, but the above case does not belong to either of them. It may be properly termed a type of pulmonic gallop rhythm.

In Case 5 there was systolic gallop rhythm of an entirely different nature, which should be called auricular systolic gallop rhythm. The author has stated already[16, 17] that auricular contraction produces a low-pitched sound caused by oscillation of the auricular wall, in any phase of the cardiac cycle. This auricular sound is transmitted better to the esophagus than to the precordium. Fig. 5*B* shows the heart sound tracing which was obtained through the esophagus at a distance of 33 cm. from the front teeth, where the left auricle is in contact with the esophageal wall. The auricular sound was clearly shown to correspond to the P wave. Systolic gallop rhythm was present only when the auricular contraction occurred in the midsystolic phase. The genesis of this auricular gallop rhythm is very different from that of any other types of systolic gallop rhythm hitherto described, and has nothing to do with the character or the movement of the aorta, or of the pulmonary artery.

SUMMARY

1. Five cases of various types of systolic gallop rhythm are reported, exclusive of the systolic click and the systolic pericardial knock.

2. One case of aortic insufficiency was regarded as belonging to common type of systolic gallop rhythm described by Potain and Wolferth and Margolies.

3. Two of the patients had mediastinal tumors. In one case the systolic gallop sound was shown to be produced by displacement of the aorta by the tumor. In the other case the systolic gallop sound was

recorded only when the pleural effusion existed. The tumor and the effusion seemed to have something to do with the occurrence of the extra sound.

4. In one case of patent ductus arteriosus and combined mitral disease, systolic gallop rhythm was present temporarily over the pulmonic area only. This extra sound appeared to be produced by the pulmonary artery or the ductus arteriosus. The author considers it a type of pulmonic gallop rhythm.

5. One case of systolic gallop rhythm of an entirely different type is reported. This gallop sound was caused by interposition of the auricular contraction in the midsystolic phase, and it should be called an auricular systolic gallop rhythm. It was most conspicuous in records made from within the esophagus.

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REFERENCES

1. Cŭffer and Barbillon: Nouvelles recherches sur le bruit de galop, Arch. gén. de méd. **1:** 129, 301, 1887.
2. Potain, P. G.: Le bruit de galop, Semaine méd. **20:** 175, 1900.
3. Wolferth, C. C., and Margolies, A.: Systolic Gallop Rhythm, AM. HEART J. **19:** 129, 1940.
4. Wiedemann, G.: Zur Frage des mesosystolischen Galloprhythmus, Ztschr. f. d. ges. exper. Med. **2:** 297, 1914.
5. Pawinski, J.: Ztschr. f. klin. Med. **64:** 70, 1907.
6. Gallavardin, L.: Pseudo-dedoublement du deuxième bruit du coeur simulant le dedoublement mitral par bruit extra-cardiaque tele-systolique surajoute, Lyon méd. **121:** 409, 1913.
7. Johnston, F. D.: Extra Sounds Occurring in Cardiac Systole, AM. HEART J. **15:** 221, 1938.
8. Lian, C., and Deparis, M.: Le Claquement meso-systolique pleuropericardique, Bull. et mém. Soc. méd. d. hôp. de Paris **49:** 496, 1933.
9. Rees, W. A., and Hughes, G. S.: Wounds of the Chest as Seen at an Advanced Operating Centre, Lancet **1:** 55, 1918.
10. Smith, S. M.: Pericardial Knock, Brit. M. J. **1:** 78, 1918.
11. Munden, W. P. H.: Pericardial Knock, Brit. M. J. **1:** 174, 1918.
12. Lister, W. A.: A Case of Pericardial Knock Associated With Spontaneous Pneumothorax, Lancet **1:** 1225, 1928.
13. Barnwell, L. B., and Greene, J.: Quoted by Johnston, F. D., AM. HEART J. **15:** 221, 1938.
14. (a) Koizumi, H.: Eine neue Methode der Registrierung des Spitzenstosses und Herztones, Nippon J. Clin. Angio-cardiolog. **4:** 137, 1938.
    (b) Koizumi, H.: Über die Verwendung einer neuen Methode der Kreislaufdiagnose mittels Anwendung von hochfrequenten electrischen Schwingungen, Klin. Wchnschr. **19:** 1109, 1940.
15. Hinohara, S.: A New Method for the Recording of Heart Sounds and Murmurs, Nippon J. Clin. Angio-cardiolog. **6:** 117, 1940.
16. Hinohara, S.: On the First Component of the Auricular Sound, Nippon J. Clin. Angio-cardiolog. **6:** 319, 1940.
17. Hinohara, S.: Investigation of the Normal Heart Sounds Induced Through the Esophagus, With Special Attention to the Auricular Sound, Nippon J. Clin. Angio-cardiolog. **6:** 159, 1940.

THE ESTIMATION OF CARDIAC OUTPUT FROM BLOOD PRESSURE AND PULSE WAVE VELOCITY MEASUREMENTS ON SUBJECTS WITH CARDIOVASCULAR DISEASE

I. Cardiovascular Disease Other Than Aortic Regurgitation

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IN A PREVIOUS report from this laboratory,[1] it was shown that the stroke volume of the heart may be calculated for normal subjects by means of empirical equations, utilizing data obtained from optical records of arterial pressure, pulse wave velocity, and shape of the pulse, together with assumed volumes for the larger arteries. Estimates of cardiac output which corresponded closely with those obtained by the acetylene method were obtained on subjects of varying size and age and in the presence of physiologic variations in the cardiovascular system induced by meals,[2] hot and cold baths,[3] and change of position.[4] The present report is concerned with the estimation of cardiac output by this method on subjects with disease of the cardiovascular system other than aortic insufficiency.

There is an obvious need for a method by which the cardiac output may be ascertained with safety and accuracy on very ill patients. Gasometric methods are often not usable in such cases.

The method is based upon estimates of the pulse pressure and of the distensibility of the arterial system. An optical oscillogram is recorded from the upper arm, from which are obtained the lateral systolic, dicrotic, and diastolic pressures. Sphygmograms are recorded simultaneously from the subclavian, brachial, femoral, and dorsalis pedis arteries, together with a cardiogram from the upper sternum. From these records are obtained the pulse wave velocities from the heart to subclavian artery, subclavian to brachial artery, subclavian to femoral artery, and femoral to dorsalis pedis artery. From the sphygmogram of the brachial pulse are calculated the duration of systole and diastole* and (utilizing the blood pressure values obtained from the oscillogram) the mean pressure, not only in the whole cycle but also in its systolic and diastolic phases. From the subject's age and surface area

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*The divisions actually used are made on an arbitrary basis.

of the body the internal cross-sectional area of the ascending aorta is estimated (utilizing a graph based upon autopsy data[1]). Then where:

V_s = Outflow from aorta in systole
V_d = Outflow from aorta in diastole
M_s = Mean pressure in systole
M_d = Mean pressure in diastole
Z = Dicrotic pressure
D = Diastolic pressure
s = Duration of systole
d = Duration of diastole
v_1 = P.W.V., heart to subclavian artery
v_2 = P.W.V., subclavian to brachial artery
v_3 = P.W.V., subclavian to femoral artery
v_4 = P.W.V., subclavian to dorsalis artery

Q = Cross section of aorta
A = Surface area of body
H = Height of body in cm.
$V_1 = Q \times 0.12H$
$V_2 = Q \times 0.15H$
$V_3 = A \times 0.065H$
$V_4 = A \times 0.34H$

$$(1)\quad V_d = \frac{12.7}{100}\left(\frac{V_1}{v_1^2} + \frac{V_2}{v_2^2} + \frac{V_3}{v_3^2} + \frac{V_4}{v_4^2}\right)(Z - D)$$

$$(2)\quad V_s = V_d\, s/d\, \frac{(M_s - 20)}{(M_d - 20)}$$

(3) Output per beat = $V = V_d + V_s$
Output per minute = Output per beat × pulse rate
$$\text{Cardiac index} = \frac{\text{Output per minute}}{\text{Surface area}}$$

The data also permit quantitative evaluation of other factors in the cardiovascular system.

1. *Effective Peripheral Resistance.*—Since the mean pressure is determined by the cardiac output and the effective resistance of the arterioles, if the first two are known, the arteriolar resistance may be expressed quantitatively, i.e., as the mean pressure divided by the cardiac index. For convenience, this value may be multiplied by 3, for, in so doing, the resultant value for normal young subjects is about 100 (70 to 130).

2. *Effective Distensibility of the Vessels.*—These measurements are obtainable from the equations, for the latter depend upon an estimation of the distensibility of the vessels which takes into account the compensatory effect of the larger aortic capacity of the older subjects. The values are expressed as the absolute increase in ml. per mm. Hg increase in pressure per square meter of body surface. They are derived from equation (1) by omitting Z-D and dividing by the surface area.

The data available on apparently normal subjects indicate that the effective distensibility of the aorta increases with age, until the age of about 40, as the result of enlargement of the aorta. Values of the order of 0.65 and 0.95 are reached; after the age of 40 or 50 these values decrease again, as changes in the walls of the vessels outbalance the effects of increased size. On the other hand, the effective distensibility of the peripheral vessels progressively decreases with advancing age in normal subjects. However, present data are inadequate for the establishment of standards.

3. *Work of the Left Ventricle.*—Since the mean pressure during the period of systolic ejection is estimated, a more accurate calculation of the compression work of the left ventricle is possible. Normal values for the compression work of the left ventricle in a man of average size may be considered as about 4,150 Gm. cm. per beat per square meter, and about 2.9 kilogram meters per minute per square meter. Some improvement can also be attained in the calculation of work done in developing kinetic energy.

4. *Time Relations of Ventricular Contraction.*—Estimation of the pulse wave velocities requires determination of the beginning of ventricular expulsion. This point may be obtained with considerable accuracy, in our experience, by recording a cardiogram from the upper sternum. Such a cardiogram also affords criteria by which the duration of the various phases of cardiac contraction may be estimated. These have additional interest when correlated with the electrocardiogram.[6]

METHODS

Estimates of cardiac output from blood pressures and pulse wave velocities were made on fifteen subjects with abnormal cardiovascular systems, fourteen of whom were patients in the medical wards of the Philadelphia General Hospital, and one of whom was a medical student. The total number of observations was twenty-four. On six of the subjects, estimates of the cardiac output by the acetylene method were also made, either immediately after or before the blood pressure measurements. On the other subjects similar estimates by the acetylene method were attempted, but the procedure proved to be beyond their capacity. The case histories of all subjects are outlined.

In most cases the subjects were examined approximately two to three hours after a light breakfast, and after at least forty-five minutes' rest. Records of blood pressure and pulse wave velocity were made in the recumbent posture, unless a semi-recumbent posture was necessitated by orthopnea. The electrocardiogram was taken on a separate camera, and was synchronized by means of a signal which marked both records simultaneously. Measurements of vessel lengths for pulse wave velocity estimates were made with the subject completely recumbent. No allowance was made for tortuosities. The cardiac output was expressed in relation to the subject's contemporary surface area, as estimated from his weight. On the other hand, the volumes of the vessels were estimated from the subject's normal, rather than contemporary, weight. The difference between the two weights was due to recent changes, usually either edema or wasting.

For acetylene estimates a mixture was used which contained a high oxygen percentage (usually over 14 per cent in the final sample after rebreathing) and an initial concentration of about 3 per cent of CO_2. Three samples were taken for analysis, usually after eighteen, twenty-four, and twenty-nine seconds of rebreathing in the more ill subjects who were incapable of deep breathing. Oxygen consumption was measured in a valveless Sanborn machine.

CASE REPORTS

CASE 1.—A male, aged 17 years, had secondary anemia, but no organic heart disease. He showed diminished exercise tolerance. He was ambulatory, but was hospitalized for study.

CASE 2.—A female, aged 24 years, had essential hypotension but no organic heart disease. She showed normal exercise tolerance and was an apparently healthy medical student. Observations were made on two occasions by both methods under basal conditions. On the second occasion the subject had had typhoid vaccine one and one-half days earlier.

CASE 3.—A male, aged 28 years, had hypertensive heart disease and cardiac enlargement. Severe congestive failure occurred eight years ago and borderline failure has been present since then. At present he is ambulatory and is taking digitalis.

CASE 4.—A male, aged 53 years, had chronic alcoholism and cardiac enlargement. He is convalescing from an attack of acute pulmonary edema which occurred two months ago. The first attack was one year ago. He was easily breathless. He was taking no digitalis.

CASE 5.—A male, aged 55 years, had arteriosclerotic heart disease, aortic sclerosis, gastric tumor, and anemia (erythrocyte count 2,900,000). He was ambulatory, but breathless on slight effort. Hypertension with mild congestive failure occurred one year ago. The patient was hospitalized for study but was given no digitalis.

CASE 6.—A male, aged 55 years, had arteriosclerotic and hypertensive heart disease, cardiac enlargement, bundle branch block, angina pectoris, and congestive failure (onset four months ago). He is convalescing, but still bedfast and taking digitalis.

CASE 7.—A male, aged 60 years, had arteriosclerotic and hypertensive heart disease, cardiac enlargement, premature contractions, and congestive failure, onset following coronary occlusion nine months ago. He is convalescing, but still bedfast and taking digitalis.

CASE 8.—A male, aged 69 years, had arteriosclerotic and hypertensive heart disease, nephrosclerosis, and cardiac enlargement. Congestive failure at present has subsided, but patient is still bedfast and is taking digitalis.

CASE 9.—A male, aged 56 years, had anginal pain on exertion, particularly in the last year. He was ambulatory, but was hospitalized for study.

CASE 10.—A male, aged 35 years, had aortic stenosis. Onset of symptoms occurred eight years ago, with acute failure two years ago and acute pulmonary congestion 2 weeks ago. He is ambulatory after past two weeks in bed.

CASE 11.—A male, aged 70 years, had hypertensive and arteriosclerotic heart disease. He was feeble and bedfast.

CASE 12.—A male, aged 69 years, had hypertensive and arteriosclerotic heart disease and was extremely feeble and bedfast. On admission one year ago blood pressure was 154/92. He has a vegetative existence in bed, and was asleep during examination (Feb. 4, 1937).

CASE 13.—A male, aged 54 years, had hypertensive and arteriosclerotic heart disease, cardiac enlargement, and congestive failure, onset three years ago with several hospital admissions in interim. Severe orthopnea occurred. The patient died three weeks later.

CASE 14.—A male, aged 48 years, had hypertensive heart disease, cardiac enlargement, and acute pulmonary edema. He was bedfast and was taking digitalis.

CASE 15.—A male, aged 59 years, had arteriosclerotic heart disease, complete heart block, alcoholism, cirrhosis, and ascites. He was bedfast and was taking digitalis.

A source of error which is to be expected is tortuosity of the vessels. The most critical test for this factor was that on Subject 5, in whom marked tortuosity could be distinguished in the abdominal aorta by palpation, and in the thoracic aorta roentgenologically. Nonetheless, the calculated cardiac index was 2.7, as compared with a value of 2.6 by the acetylene method. (Another case of marked tortuosity was Subject 8. Here the two estimates were discrepant, but the high value obtained by acetylene, though substantiated by all three samples, is likely to have been due to excitement.) It seems probable, therefore, that the errors which are certainly present in subjects with tortuous vessels tend to cancel one another. In such subjects the pulse wave velocities must be underestimated, and the consequent errors would appear in the denominators where the values are squared. However, the volumes of these vessels, which appear in the numerators, would also be in error due to underestimates (a) in the length of the vessels and (b) in their diameter, for abnormal increases in diameter are likely to accompany tortuosity in the central vessels. If the two errors in the numerators are proportional to the tortuosity, the errors due to this factor are squared in both numerator and denominator, and are likely to cancel out.

RESULTS

Validity of the Method of Estimation by Calculation From Blood Pressure.—In Table I values are given for those subjects on whom estimates of cardiac output were made by both methods. The agreement between the two methods is fair. The mean deviation of the calculated estimate from that obtained by the acetylene method was ±14 per cent of the latter; the average estimate by calculation was 2.35 liters/m²/min., and that by acetylene, 2.33. The mean deviation between the two methods in normal subjects has averaged ±12 per cent. The method of calculation appears to have no new inherent errors in these cases.

In Table II the subjects are arranged in different groups, and within each group in the apparent order of their decreasing fitness.

Ambulatory Subjects.—Subject 3 had values for both the output and work of the left ventricle which were above average normal. Clinical examination likewise revealed no evidence of circulatory insufficiency at rest, although marked breathlessness occurred during physical exertion. Apparently the recorded output and work of the left ventricle were the approximate maximum obtainable, and could not be sufficiently increased to accommodate additional physiologic requirements. The estimated distensibility of the aorta appeared to equal the maximal normal values at any age.

Subject 5, like Subject 3, exhibited normal values for the output and work of the left ventricle. This was apparently attained, however, to a considerable extent by enlargement and tortuosity of the aorta.

Subject 9 had low values for distensibility of the large vessels which reflected, in this case, an advanced degree of aortic disease.

TABLE I

NO.	SEX	AGE	HEIGHT (CM.)	WEIGHT (KG.)		SURFACE AREA (SQ. M.)	OXYGEN CONSUMPTION (ML. PER MIN.)	A-V OXYGEN DIFFERENCE (ML. PER LITER)	CARDIAC INDEX BY ACETYLENE	CARDIAC INDEX BY CALCULATION	PULSE RATE	CLINICAL SYSTOLIC PRESSURE	BLOOD PRESSURES (LATERAL)
				ACTUAL	NORMAL								
1	M	17	163	45.8		1.45	252	52	3.3	2.8	81	105	97/50
2	F	24	165	55.3		1.59	173	69	1.6	1.55	61	84	81/58
							195	47.5	2.6	2.8	73	85	79/46
3	M	28	163	62.8		1.68	223	62	2.15	2.45	81	127	124/90
4	M	53	184	70.4		1.92	218	52	2.2	1.7	70	79	75/48
5	M	55	171	51.8	68.0	1.61	193	45	2.70	2.6	98	104	100/67
6	M	55	174	67.0		1.79	203	68	1.65	1.85	62	108	104/74
7	M	60	178	85.6	98.0	2.01	291	69	2.05	2.3	37	169	165/66
											84	122	113/86
8	M	69	175	62.2	73.0	1.75	219	44	2.9	2.05	71	173	162/93

Average values of cardiac index were 2.35 and 2.23. Mean deviation of calculated value from acetylene value was +14 per cent.

TABLE II

OBSERVATIONS	AMBULATORY PATIENTS				OLD AGE (BEDFAST)				HYPERTENSION				CARDIAC IRREGULARITIES	
	3	5	9	10	8	11	12		13	14		15	7	
							1/7/37	2/4/37		11/5/36	11/12/36		SLOW	FAST
Age (years)	28	55	56	35	69	70	69	69	54	48	48	59	60	60
Mean pulse rate	81	97	93	97	71	84	67	*49*	72	115	106	*34*	*37*	*84*
Clinical systolic pressure	127	104	138	92	173	216	137	119	201	132	117	156	169	122
Lateral pressures	124/90	100/67	135/81	89/68	*169/93*	*212/104*	*127/67*	*111/57*	*197/112*	*128/100*	*109/82*	*147/57*	*165/65*	*113/86*
Mean pressure	105	83	105	78	133	157	95	76	149	114	94	94	120	99
Mean pressure in systole	114	88	117	81	146	184	113	94	171	118	98	103	142	107
P.W.V. heart to subclav.	2.15	4.55	4.75	3.7	*7.75*	*10.0*	*7.05*	*5.4*	4.65	5.55	4.45	4.85	4.1	3.35
Subclav. to femoral	6.0	6.2	*12.0*	5.9	*17.7*	*23.9*	*11.2*	*10.85*	*12.3*		*9.65*	5.95	8.75	8.85
Subclav. to brachial	10.1	8.9	7.85	7.3	7.2	*12.8*	7.8	8.25	*16.3*	*12.7*	*9.2*	5.8	9.15	8.3
Femoral to dorsalis	10.25	9.7		8.0	9.8	*15.75*	11.8	10.75	*17.2*		*26.1*	12.55	9.35	7.3
Effect of distension of aorta	*0.96*	0.55	*0.38*	0.50	*0.15*	*0.08*	*0.22*	*0.33*	*0.34*		0.34	0.49	0.55	0.76
Effect of distension of peripherial artery	0.08	0.11		0.13	0.11	0.04	0.08	0.09	*0.03*		*0.03*	0.09	0.11	0.17
Cardiac index	2.45	2.35	(2.50)	*2.05*	*2.05*	*1.3*	*1.2*	*1.15*	*2.25*		*1.30*	*1.8*	*2.50*	*2.15*
Stroke vol./sq. m.	30	24	27	21	29	*15*	*18*	23	31		*12*	*53*	*68*	*26*
Effect of peripheral resistance	127	105	(126)	78	*196*	*362*	*238*	*195*	*200*		*212*	153	144	137
Duration of Q-T (elect. systole)	0.339		0.377	0.320	0.387	0.335	0.348		0.470	0.365	0.325	0.500	*0.396*	*0.404*
Duration of mech. systole*	0.336	0.302	0.372	0.330	0.355	0.275	0.308	0.328	0.305	0.251	0.260	0.422	*0.340*	*0.342*
Compress. work lt. vent/ beat/sq. m.	4,730	3,030	3.840	>2,100	*5,700*	3,320	2,800	2,960	*6,250*		1,560	*7,440*	*13,100*	*3,730*
Compress. work lt. vent/ min./sq. m.	3.85	2.95	3.55	>2.05	*4.1*	2.8	*1.8*	*1.5*	*4.5*		*1.65*	2.95	*4.85*	3.15

Attention is drawn by italics to the data considered of greater significance.
*Measured from the start of rising tension time to the second sound.

Subject 10, whose clinical examination revealed aortic stenosis, had a relatively low cardiac output in spite of a probably high work level of the heart. (An accurate estimation of the work of the heart could not be obtained in the presence of the valvular lesion.) The peripheral vascular system appeared normal.

Hypertensive Subjects of the Old-Age Group.—The three, elderly, hypertensive subjects (8, 11, and 12), who were bedfast, formed a strong contrast with the ambulatory group. In all cases the effective distensibility of the aorta was low. The effective distensibility of the more peripheral vessels did not appear particularly low (except in Subject 11), but these values may have resulted from underestimation of the pulse wave velocity due to tortuosity of the arteries.

The effective peripheral resistances were high. The cardiac output was low in Subjects 11 and 12. In Subject 8 the cardiac index was 2.05, but this value was likewise low when considered in relation to the increased work of the left ventricle. The low cardiac output can probably be correlated with the extremely feeble and apathetic condition of these patients.

The blood pressure in Subjects 8 and 11 was high. In Subject 12 the blood pressure was normal, but hypertension was nevertheless an etiologic factor. This case illustrates how hypertension can be masked by a low cardiac output, although the distensibility of the aorta is subnormal and the peripheral resistance is high.

Subject 12 suffered from frequent attacks of paroxysmal nocturnal dyspnea. A possible cause for these attacks was demonstrated when the patient fell asleep during a repetition of his examination. Sleep was accompanied by marked slowing of the heart rate. The already low cardiac output thereupon sustained a further decrease, until the cardiac index was only 1.15.

Hypertension in the Middle-Aged Group.—The data on these subjects show certain quantitative differences from those in the previous group. Reduction in distensibility was found chiefly in the peripheral arteries, and was relatively less pronounced in the aorta. The cardiac output was very low in Subjects 14 and 15, and this could be correlated with the more severe symptoms of these patients, as compared with Subject 13, who had a normal cardiac output. Subject 13, however, was the only patient who died within three weeks of his examination. His higher level of cardiac work, by exerting an excessive strain on the heart, may have been more harmful than the low cardiac outputs of the other two distressed, but still living, subjects.

Cardiac Irregularities.—Subject 15 had complete heart block. The slow heart rate resulted in a large stroke volume and a high level of cardiac work per minute.

Subject 7 had ventricular premature contractions which produced a very irregular pulse rate, with periods in which the rate was 37 (due

to pulse deficit), other periods in which it was 84, and still others in which it alternated rapidly between the two levels. The values observed under the two main conditions are shown in Table II. Estimates of the cardiac output were probably not much in error, for they gave a cardiac index of 2.3, whereas the acetylene method gave one of 2.05.

A series of pulse curves illustrating the shift from the slow pulse, when extrasystoles were present, to the rapid pulse, when extrasystoles were absent, is reproduced in Fig. 1, together with simultaneous electrocardiograms.

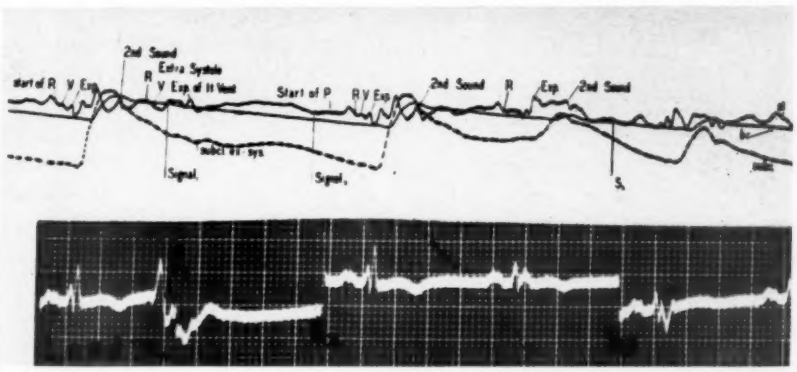

Fig. 1.—Records of sternal pulsation and subclavian (dotted line) and brachial pulses of Subject 9 during the change from the slow pulse to the fast pulse, redrawn and reduced (about ⅓) to the same time relations as the electrocardiogram which was taken simultaneously. The latter is shown below. Corresponding points on the two records are indicated as signals S_1, S_2, and S_3; at these points the electrocardiogram is changed in level. Pulse 2 is of ventricular origin; it is not preceded by a P wave. The later pulses at the faster pulse rate are noteworthy for very long and abnormal QRS complexes. The pressure levels of the two types of pulse are indicated in Table II; the intervals between the start of R and the subclavian pulse are indicated in Table III.

TABLE III

TYPE OF PULSE	DURATION OF QRS (SEC.)	START OF R TO SUBCLAVIAN (SEC.)	START OF R TO START OF CONTRACTION (SEC.)	RISING TENSION TIME (SEC.)	START OF EJECTION TO SUBCLAVIAN PULSE (SEC.)
Large slow beats	0.099	0.135	0.022	0.062	0.051
Small fast beats	0.154	0.206	0.023	0.121	0.062
Premature contractions	0.230	0.275	0.042	0.190	0.043

The sequence of events may be followed from these records and the data in Table III. With the slow pulse and the long rest between normal beats, conduction was fairly adequately accomplished, and the QRS complex was not very abnormal. The stroke volume and the cardiac work were very high. The change to a more rapid pulse, without extrasystoles, lessened the load as far as heart work was concerned, but left little time for recovery of the conducting tissue; the QRS complex became grossly lengthened and abnormal in shape. The time relations

allowed the conclusion to be drawn that the delayed conduction, on which the abnormal complex depended, was affecting the left ventricle, and also that the origin of the premature beats was in the right ventricle.

The time relations which were observed merit brief discussion. The faster pulse beats, as well as the premature contractions, were associated with a much increased duration of the QRS complex, and also with a great exaggeration of the interval between the start of the R wave and the subclavian pulse. The increases in these two intervals were approximately of the same order, and not open to question. Although the sternal pulsations were *interpreted* as indicating an abnormally long period of rising tension time in the left ventricle, such deductions were not essential to the argument. There was unquestionable evidence of asynchronism of the two ventricles. The auricular contractions were also often abnormal or not synchronized, for the P wave was commonly notched or double (Fig. 1); accompanying the double P wave there was a duplication of the auricular wave in the sternal pulsation.

DISCUSSION

The data presented give evidence that the method of estimating cardiac output from blood pressure measurements can be applied without serious errors to patients with cardiovascular disease other than aortic incompetence.[5] It is probable that it would be inapplicable to patients with aneurysms, although this has not been investigated.

Calculation of the work of the left ventricle demonstrated that the additional work which was required in order to maintain the cardiac output could not be accomplished without a considerable increase in the oxygen consumption of the heart. If the oxygen is supplied to the heart at a normal tension, there must also be a considerable increase in the coronary flow. Such data are in agreement with Rasmussen's[7] demonstration that there is an increased oxygen usage in hypertensive subjects. If the oxygen intake and cardiac output are normal or subnormal in such patients, one must assume that this increased utilization by the heart is accompanied by a considerable deficiency in the supply of blood and oxygen to the peripheral tissues.

Cardiac indices of the same order as those here reported were found by Grollman, et al.,[8] in cases of congestive failure. The average in their eight cases was 1.87, with extremes of 1.29 and 2.25; the average of the values obtained by calculation in the eleven cases of congestive failure here described was 1.72, with extremes of 1.15 and 2.25. The higher cardiac outputs observed in this series occurred in patients who appeared capable of maintaining a relatively high grade of mental or physical activity. Such activity may, however, be attainable only at the expense of an excessive load on the heart (Subject 13). A low cardiac output may be associated with evidence of considerable damage to the peripheral vascular system (Subject 14), or with low activity and a vegetative existence, with no indication of any progressive development of symptoms of congestive failure (Subject 12). In such cases the work performed by the heart may be markedly subnormal.

Analysis of the type which we have described enables one to recognize hypertension in subjects who have no hypertension (either systolic or diastolic) at the time of examination (Subjects 12 and 14). Comparison of the middle-age and old-age groups gives some indication that the method might distinguish between hypertensive subjects of different types. Analysis of irregular heart action, with pulses at various pressure levels, can be attained, and affords evidence as to which side of the heart is affected mainly by deficient ventricular conduction, as well as to the site of origin of premature ventricular contractions. The principles discussed by Katz, et al.,[9] and by Braun-Menendez and Solari[10] are applicable to the records obtained.

CONCLUSIONS

1. It is shown that the stroke volume of the heart may be calculated from measurements of pulse pressure and pulse wave velocity on patients with various types of cardiovascular disease (except aortic regurgitation) without apparent, serious error.

2. The applicability of the method to subjects with tortuous vessels (which would appear likely to introduce serious errors) is attributed to the introduction of errors of approximately uniform extent in both the numerators and denominators of the equations.

3. The method is utilized to calculate the work of the left ventricle. In cases of hypertension in which the cardiac output is well maintained, the work which the heart has to perform is shown to be high. It is demonstrated that, unless this work is performed under very unfavorable circumstances, it must be accompanied by an increased oxygen intake by the subject and by an increased coronary circulation. A normal oxygen intake and a normal cardiac index in such patients do not, therefore, indicate a normal and adequate supply of oxygen and blood to the peripheral tissues.

4. Attention is drawn to the development of decreased distensibility of the large vessels in two groups of patients, namely, an older group with the changes mainly in the aorta, and a middle-age group with the changes mainly in the peripheral arteries.

5. It is shown that hypertension in cases in which there is temporarily no hypertension, because of a low cardiac output, may be recognized by such analysis, even when the blood pressure is normal.

We should like to take this opportunity to thank the staff of the Philadelphia General Hospital and, in particular, Dr. William E. Robertson, whose cooperation made this work possible. Our thanks are also due to the Faculty Research Committee of the University of Pennsylvania for financial assistance in this research.

REFERENCES

1. Bazett, H. C., Cotton, F. S., Laplace, L. B., and Scott, J. C.: The Calculation of Cardiac Output and Effective Peripheral Resistance From Blood Pressure Measurements With an Appendix on the Size of the Aorta in Man, Am. J. Physiol. **113**: 312, 1935.

2. Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D.: Calculation of Cardiac Output From Blood Pressure Measurements Before and After Meals, Am. J. Physiol. **116**: 551, 1936.
3. Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D.: Effect of Baths at Different Temperatures on Oxygen Exchange and on the Circulation, Am. J. Physiol. **119**: 93, 1937.
4. Scott, J. C., Bazett, H. C., and Mackie, G. C.: Climatic Effects on Cardiac Output and the Circulation in Man, Am. J. Physiol. **129**: 102, 1940.
5. Bazett, H. C., Laplace, L. B., and Scott, J. C.: AM. HEART J. **22**: 749, 1941.
6. (a) Bazett, H. C.: Analysis of the Time Relations of Electrocardiograms, Heart **7**: 353, 1920.
   (b) Bazett, H. C., and Sands, J.: The Significance of Measurements of the Duration of Systole, Ann. Clin. Med. **5**: 190, 1926.
7. Rasmussen, H.: Über den Grundumsatz bei essentieller Hypertonie, Acta med. Scandinav. **93**: 594, 1938.
8. Grollman, A., Friedman, B., Clark, G., and Harrison, T. R.: XXIII. Studies in Congestive Heart Failure. A Critical Study of Methods for Determining the Cardiac Output in Patients With Cardiac Disease, J. Clin. Investigation **12**: 751, 1933.
9. Katz, L. N., Landt, H., and Bohning, A.: Delay in Onset of Ejection of Left Ventricle in Bundle Branch Block, AM. HEART J. **10**: 681, 1935.
10. Braun-Mendendez, E., and Solari, L. A.: Ventricular Asynchronism in Bundle Branch Block, Arch. Int. Med. **63**: 830, 1939.

THE ESTIMATION OF CARDIAC OUTPUT FROM BLOOD PRESSURE AND PULSE WAVE VELOCITY MEASUREMENTS ON SUBJECTS WITH CARDIOVASCULAR DISEASE

II. Aortic Regurgitation

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IN PART I of this report,[1] it was shown that the method of calculating the stroke volume of the heart from measurements of pulse pressure and pulse wave velocity[2] is applicable to patients with various types of cardiovascular disease other than aortic regurgitation. The method is not applicable to patients with aortic regurgitation because the pulse pressure is determined by the volume of blood which returns to the left ventricle, in addition to that which proceeds through the aorta. The values obtained, therefore, do not represent the effective stroke volume.

If the cardiac output in a patient with aortic regurgitation is measured by the acetylene method, a comparison of the values so obtained with those obtained by somewhat modified calculations from the pulse pressure supplies an estimate of the degree of regurgitation. This, in turn, permits investigation of the nature and extent of the physiologic handicap which aortic regurgitation imposes upon the heart. The observations to be reported are concerned with the results of this procedure as applied to two subjects.

METHODS

The procedure used in estimating the cardiac output by the acetylene method, as well as the technique employed in obtaining the data used in the equations, was the same as that already described.[1]

The method of calculation[2] required certain changes, for the outflow from the aorta in diastole occurs both into the smaller vessels and, by regurgitation, into the ventricle, whereas in systole it occurs only into the vessels. The following modification was used:

The calculation is made in the ordinary way from the fall of pressure in diastole. This gives the blood leaving the aorta for the capillaries (V_d), and also the regurgitating blood (x).

$$(4) \qquad V_d + x = \frac{12.7\ (Z\text{-}D)}{100}\left(\frac{V_1}{v_1^2} + \frac{V_2}{v_2^2} + \frac{V_3}{v_3^2} + \frac{V_4}{v_4^2}\right)$$

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V_d and x cannot be distinguished. Equations (*2*) and (*3*), which were given in Part I,[1] may be combined as follows:

$$(5) \qquad \frac{V}{V_d} = 1 + \frac{s}{d} \frac{(Ms - 20)}{(Md - 20)}$$

If V be determined by the acetylene method, V_d may be calculated by equation (*5*). If V_d be subtracted from the value determined by equation (*4*), the value of x is obtained.

Two subjects who had aortic regurgitation were studied.

CASE 1.—A male, aged 40 years, had syphilitic heart disease. The heart was greatly enlarged; rhythm was normal. He had angina pectoris and had had congestive failure, onset two years previously, with several hospital admissions in the interim. He was confined to bed and digitalized.

CASE 2.—A male, aged 26 years, had rheumatic heart disease. There was extreme cardiac enlargement. Rhythm was normal. The patient had no symptoms of cardiac insufficiency and played basketball without discomfort. No medication was administered.

Subject 1 was studied two hours after a light breakfast; Subject 2, under basal conditions.

RESULTS

A summary of the values obtained on the two subjects is included in Table I.

In Subject 1, the effective stroke volume by the acetylene method (somewhat doubtful because of difficulties in breathing) was 67.4 ml.; the true V_d was 28.9 ml., and x was 13.4 ml. Apparently, therefore, there was with each contraction of the left ventricle an expulsion of 80.8 ml., of which 13.4, or 16.6 per cent, regurgitated during diastole. The distensibilities of the large vessels were subnormal, i.e., 0.36 ml./m²/mm. Hg for the two central sections, and 0.10 for the two more peripheral. (The normal values for these distensibilities in subjects up to 40 years of age are about 0.52 and 0.14.) The blood pressures were high, and the work of the left ventricle was therefore much increased as the result of all these factors, in spite of the moderate degree of regurgitation. The compression work was calculated as 16,000 Gm. cm. per beat, and as 11.8 kilogram meters per minute, as compared with normal levels of about 6,900 (4,150 per square meter) and 4.85 (2.9 per square meter). The extra work would necessitate the use of an additional 17 ml. of oxygen per minute (assuming a mechanical efficiency of 1 to 5) and an additional coronary flow of some 300 ml. per minute (assuming an oxygen utilization of 55 ml. per liter). The actual increases should be greater, for any increase in basal metabolism would require, also, an increased flow through the skin for heat loss. If the mechanical efficiency of the heart were lowered by myocardial changes, the increase in metabolism would also have to be greater. Consequently, a normal cardiac index is

TABLE I

SUBJECT NO.	SEX	AGE (YR.)	HEIGHT (CM.)	WEIGHT (KG.)		SURFACE AREA (SQ. M.)	OXYGEN CONSUMPTION PER MINUTE (ML.)	ARTERIO-VENOUS OXYGEN DIFFERENCE (ML. PER LITER)	CARDIAC INDEX BY ACETYLENE	CARDIAC INDEX BY CALCULATION (UNADJUSTED)	PULSE RATE	CLINICAL SYSTOLIC PRESSURE	ESTIMATED LATERAL BLOOD PRESSURES
				ACTUAL	NORMAL								
1	M	40	166	61.2	73.0	1.66	246	48.5	3.0	4.4*	74.0	181	172/72
2	M	26	178	76.8		1.95	337	46.8 56.5	3.7 3.05	8.05*	69.3	164	151/49

*The cardiac outputs here given are those calculable by the method as if no aortic lesion were present. The gross exaggeration that results is obvious. For calculation of the amount regurgitated see text.

not to be anticipated in such cases, and, even if it were normal, it would not indicate a normal peripheral circulation.

In Subject 2, the values were even more striking. This subject was relatively fit (playing college basketball), and had an enormous heart. An orthodiagram showed that the transverse diameter of the heart was 17.5 cm. in a thorax 26.1 cm. in diameter.

At the time when the observations were made, the subject was somewhat excited, and the acetylene procedure was consequently carried out twice, before and after obtaining blood pressure records. The pulse rate was at first 74 to 78, later, 52 to 67. The diastolic pressures indicated in Table I appear high as compared with the auscultatory estimates usually used in such cases. The diastolic pressure was not measurable in this subject by auscultation; the apparent level was zero.

If the mean values for cardiac output (6.57 liters) and for pulse rate (69.3) are used, the real stroke volume is calculated as 96.2 ml. From the blood pressure data a regurgitation of 41.7 ml. is estimated. The left ventricle therefore ejected 137.9 ml., of which 31 per cent regurgitated. The distensibility of the vessels was high, namely, 0.56 ml./mm. Hg/m^2 for the central, and 0.23 for the peripheral, vessels. The high degree of regurgitation and the high systolic pressure gave high estimates for the compression work of the left ventricle, namely, 23,000 Gm. cm./beat and 16.0 kilogram meters/min., as compared with normal values for a subject of this size of about 8,100 and 5.6, respectively. The large amount of blood expelled in systole also implied a high mean velocity in the aorta of about 138.5 cm./sec., so that the work of developing kinetic energy must have been also quite high. This work may be calculated on the assumption of a uniform velocity of expulsion, and the actual work is, on such a calculation, certainly underestimated. It may also be calculated on an assumption of a constant rate of shortening of circular fibers surrounding a spherical ventricle. Assuming a final internal diameter of 2 cm. for the "emptied" left ventricle, one may calculate an initial diameter of 6.5 cm. The cross-section area of the aorta was assumed to be 2.77 cm.,^{2} and the duration of ejection was 0.36 sec. Calculation of the work involved in producing kinetic energy was 1,425 Gm. cm./beat on the assumption of a constant velocity of ejection, and 2,875 on that of a constant rate of muscular shortening. The real value probably lies between these two estimates.

The increased work of production of kinetic energy above a probable normal level on the two assumptions was 1,260 Gm. cm. per beat on the first, and 2,600 on the second. The total work of the left ventricle may be calculated as exceeding the normal by 675 to 732 kilogram meters per hour. If the same assumptions are made as for Subject 1, an additional oxygen consumption of 27 to 30 ml. per minute must be expected, which should give a total basal oxygen consumption of 296 to 299 ml. The observed value at the time of examination was 337, and, on

the next morning, when the subject was more relaxed, 286. The increased coronary flow to be anticipated would be 500 to 550 ml./minute. The data indicate that, whereas under normal basal conditions the heart is likely to consume 8 to 9 per cent of the total oxygen utilized, this proportion may be readily doubled when the heart is abnormal.

Other approximate calculations may be made on Subject 2. The work of inducing kinetic energy in the left ventricle was 5.8 to 10.7 per cent of the total work of this ventricle (according to the assumptions adopted), as compared with 2.0 to 3.3 on similar assumptions for a normal subject. The difference would be much greater under nonbasal conditions. If normal pressures be assumed for the pulmonary artery, the relative work of the two ventricles may be calculated. Whereas in the normal subject the work of the left ventricle is about twice that of the right, in Subject 2 the ratio was about 3:1. This may be compared with the relative weights of the ventricles in such cases. Lewis[3] reported a normal ratio for LV/RV of 1.81, and ratios as high as 2.74 and 3.44 in cases of aortic regurgitation of an extreme degree.

SUMMARY AND CONCLUSIONS

In patients with aortic regurgitation, the degree of regurgitation may be estimated from the difference between values for cardiac output made by the acetylene method and a modification of the method of calculation from pulse pressure and pulse wave velocity. By this procedure, the regurgitation was found in two subjects to amount to 13.4 and 41.7 ml., respectively.

From data obtained in this study, it appears that the presence of free aortic regurgitation may double the oxygen utilization of the heart, and require an increase of over 500 ml. per minute in the coronary blood flow. The work of the left ventricle may be increased by approximately 50 per cent or more.

REFERENCES

1. Bazett, H. C., Laplace, L. B., and Scott, J. C.: The Estimation of Cardiac Output From Blood Pressure and Pulse Wave Velocity Measurements on Subjects With Cardiovascular Disease. I. Cardiovascular Disease Other Than Aortic Regurgitation, AM. HEART J. 22: 737, 1941.
2. Bazett, H. C., Cotton, F. S., Laplace, L. B., and Scott, J. C.: The Calculation of Cardiac Output and Effective Peripheral Resistance From Blood Pressure Measurements With an Appendix on the Size of the Aorta in Man, Am. J. Physiol. 113: 312, 1935.
3. Lewis, T.: Observations Upon Ventricular Hypertrophy With Special Reference to Preponderance of One or Other Chamber, Heart 5: 367, 1914.

A RECORD CASE OF THE TETRALOGY OF FALLOT, WITH COMMENTS ON METABOLIC AND PATHOLOGIC STUDIES

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FOR more than a decade, anoxemia has been of special interest in certain of the laboratories from which this report originates. The first and probably the only D'Oeagne nomogram ever constructed of the acid-base balance of the blood of a patient with congenital heart disease and cyanosis was based upon data collected at the Massachusetts General Hospital in 1925.[1] Subsequent communications have been concerned with the effect of (a) a diminished oxygen percentage on normal subjects at sea level,[2] (b) a diminished partial pressure of oxygen on temporary residents in the Colorado Rockies at 10,000 and 14,000 feet,[3] (c) a diminished partial pressure of oxygen on temporary residents in the Chilean Andes at altitudes as high as 20,100 feet,[4] and (d) a diminished partial pressure of oxygen on permanent residents in the Andes.[5] The unsaturation of arterial blood with oxygen and a diminished transport of oxygen to the tissues were the common denominator in all of the studies.

Because of the desire to enhance our knowledge of the effects of prolonged anoxemia at a barometric pressure corresponding to sea level conditions, we have collected extensive metabolic data on a patient who suffered from cyanotic congenital heart disease for nearly twenty years. A comprehensive post-mortem examination confirmed the clinical diagnosis of tetralogy of Fallot. The patient was seen in our hospital for the first time at the age of 18, and stated that his lips had been blue since the age of 2. He was an intelligent, cooperative, and, at that time, ambulatory patient, and agreed to participate in a metabolic experiment. He was transferred, therefore, to the research ward and remained for approximately a month. He was readmitted to the hospital on three occasions. At all times he was under the medical supervision of members of the medical and cardiac clinics. Subacute bacterial endocarditis was suspected at various times, but the blood cultures invariably were

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reported as showing no growth. Terminally, the patient suffered from a large cerebral abscess. Detailed acid-base studies with other metabolic data on a patient with congenital heart disease are not often available. These observations, together with a post-mortem report, permit one to designate the complete study as unique.

REPORT OF CASE

D. B., Massachusetts General Hospital Unit No. 91316, a Grecian-born school boy, aged 18 years, was admitted to the Massachusetts General Hospital on Nov. 5, 1937, complaining of dyspnea, orthopnea, a dry cough, and weakness for three weeks.

Family History.—His father, mother, sister, and brother were living and well. Congenital, hereditary, and cardiac stigmas were denied.

Past History and Present Illness.—The patient was apparently normal and well until he was stricken with diphtheria at the age of 2. Careful questioning of the parents failed to elicit any history of cyanosis prior to this illness. After the attack of diphtheria his lips became blue and remained blue during the following seventeen years. For several years prior to the hospital admission his parents believed that he had been more cyanotic than immediately before admission. Between the ages of 2 and 5 he suffered from sudden attacks of syncope. Thereafter he was free from them, and entered school, where he progressed without difficulty until the age of 9. At that time he had a severe attack of tonsillitis. This was followed by swelling of the ankles and knees. He maintained that he was paralyzed during this illness, but it is more likely that he was incapacitated by rheumatic polyarthritis. Recovery was slow, but eventually he was able to return to school with no residual joint dysfunction. His physical activity was curtailed, however, and the strenuous sports engaged in by boys of his age were forbidden.

Each winter he suffered from one or more attacks of tonsillitis, with little or no fever or other constitutional symptoms. His voice became "adenoid" in quality, and he was able to breath only through his mouth. There was recurrent swelling of his ankles during the day, and they became tender when he was fatigued. Frequency of urination during the day and enuresis at night were troublesome. He carried on his school work without difficulty, and maintained a scholastic standing near the top of his class. Three years before admission he had an acute, left middle-ear infection which was followed by a purulent discharge. The discharge recurred frequently, and loss of acuity of hearing eventually developed. He also had, two or three times a year, sudden attacks of earache, severe dizziness, and vomiting, and would fall to the ground. Five weeks before admission, after climbing the stairs to his classroom, he experienced acute dyspnea, became weak, and for several minutes was partially apneic. After an attack of unproductive coughing he felt somewhat better; he had a frontal headache, but continued with his school program. Three days before admission the dyspnea became unbearable; he was compelled to remain at home, and finally decided to enter the hospital.

Physical Examination.—Examination showed that the patient was moderately well developed, but rather poorly nourished. There was general cyanosis, which was most marked in the lips and nails, but was also evident in the skin over the entire body. The ocular fundi showed hazy disc margins; the veins were markedly dilated, whereas in the periphery the arteries were narrow. No retinal exudates or hemorrhages were seen. The sinuses were dark on transillumination. Both nares showed considerable crusting. The tonsils were hypertrophied and showed evidence of chronic infection. Both aural canals contained foul-smelling, thick pus. The drums

had been destroyed. The hearing was slightly impaired. There was a left dorsal scoliosis, with a right dorsal lumbar curve, and moderate kyphosis was present. The chest was barrel-shaped. There was a precordial bulge. Many dilated veins were visible. Examination of the heart by Dr. Edward Bland was reported as follows: "The heart showed well-marked enlargement, with prominent systolic pulsations to the right as well as to the left of the sternum. No thrill was palpable. On auscultation there were (1) prolongation and reduplication of the first sound over the lower cardiac area, and (2) a moderately loud and long, early, diastolic murmur which was widely transmitted, but was best heard along the left sternal border. There was a slight systolic blow at the apex. The pulmonary second sound was present, but was not remarkable. Fluoroscopic examination showed (1) well-marked cardiac enlargement, with the general configuration of right ventricular hypertrophy, (2) a full-sized, dynamically pulsating aorta, and (3) absence of unusual prominence of the pulmonary conus, and normal hilus shadows without a hilus dance. In the right anterior oblique view there was but slight encroachment on the posterior mediastinal window." The blood pressure was 116/84 in the arm and 120/84 in the leg. Examination of the abdomen was negative.

There was marked soft tissue clubbing of the fingers and toes. The knees showed soft tissue swelling and were tender on palpation. There was no limitation of motion. There was slight edema of the shins and ankles. There were marked tortuosity and engorgement of the leg veins.

Partial Laboratory Data.—The hemoglobin measured 140 per cent by the Sahli method; the erythrocyte count was 8,660,000; and the leucocyte count was 5,900. No satisfactory blood smear or differential count of the leucocytes was obtained because of the great number of erythrocytes. The Hinton reaction on the blood was negative. The basal metabolic rate on two occasions was +1 and +5 per cent, respectively. The vital capacity was 2.6 liters.

Casual specimens of urine showed a maximum specific gravity of 1.018 and a trace of albumin, but no sugar or diacetic acid. Examination of the centrifuged specimen showed several erythrocytes, a few leucocytes, and occasional hyalin and granular casts. A urine concentration test after abstinence from fluid for twelve hours showed a maximum specific gravity of 1.018. This value is corrected for the protein which was present. The excretion of phenolsulphonphthalein, injected intravenously, was 20 per cent in fifteen minutes, and totaled 30 per cent in one hour. Two blood cultures were negative for pathogenic organisms.

The venous pressure* was 80 mm. of water by the Moritz and Tabora method. Measurement of the circulation time following the intravenous injection of 10 c.c. of decholin gave discordant results and a doubtful end point. At the first determination the end points were thirty-five and fifty-six seconds, respectively (normal, ten to sixteen seconds). At the second, they were twenty-six and thirty-four seconds, respectively. The respiratory minute volume was 7.7 liters. The oxygen consumption per minute was 244 c.c., and the respiratory quotient was 0.85.

The electrocardiogram showed marked right axis deviation, unusually large P waves, and a P-R interval of 0.20 second.

Roentgenologic Examination.—The following interpretations were reported by Dr. A. O. Hampton: "There is marked thickening of the mucous membranes of both antra. There may be a small amount of fluid on the left side. The ethmoids show some thickening of the mucous membranes. The frontal sinuses are underdeveloped. There is sclerosis of both mastoids. The heart is grossly enlarged and rounded in shape. The greatest enlargement appears to be in the region of the auricles and the right ventricle. The pulmonary conus and pulmonary vessels are

*We are indebted to Dr. C. Sidney Burwell for the measurements described in this paragraph.

relatively small. The shadow of the superior vena cava appears large. The size of the aorta is greater than normal. Both auricles are dilated in the oblique view. Appearance is that of congenital heart disease of a rather unusual type. The most unusual features are enlargement of the aorta and absence of dilatation of the pulmonary vessels. An intravenous pyelogram shows the kidney outlines to be considerably larger than normal and smooth in outline. The dye is excreted poorly. The kidney pelves and calices are not distinctly seen; they are small and show a suggestion of multiple pressure defects. The appearance is similar to that of polycystic kidneys. The phalanges of the hands and feet are long and tapering, especially the terminal portions. There is no bony clubbing and no periosteal reaction. There is some thickening of the terminal soft tissues. The structure of the bones appears normal."

Subsequent Course.—The patient was readmitted to the hospital three times during the following year. A diminishing cardiac reserve was responsible for the second admission, on Feb. 16, 1938. The blood pressure was 100/65. A blood culture was negative. He was discharged as somewhat improved.

The third admission, March 15, 1938, was necessary because of an acute enteritis. The cardiac state was thought to be unchanged at that time. Several urine specimens showed erythrocytes and leucocytes, albumin, and a few granular and hyalin casts. The leucocyte count varied between 4,000 and 6,700. Two stools showed a positive guaiac test, and three, a negative. Three blood cultures were negative. A tentative diagnosis of subacute bacterial endocarditis was based upon the following evidence: cardiac disease, hematuria, fever, pleural pain (from pulmonary embolism?), and possible mesenteric thrombosis.

The fourth admission, Nov. 14, 1938, was five days before death. A greater part of the intervening time had been spent in bed, but in moderate comfort. At one time, pains in the elbows, wrists, and knees were distressing. It was undecided whether this was caused by acute rheumatic fever or pulmonary osteoarthropathy. There were two attacks of chest pain which were thought to have been associated with pulmonary infarcts. Five days before admission a severe headache developed. This was largely responsible for his return to the hospital.

Physical Examination.—The pulse rate was 80 per minute, and the pulse was regular. The blood pressure was 110/70. The heart examination was as described on the first admission. The lungs were clear and resonant. The edge of the liver was felt 3 cm. below the costal margin, and was slightly tender. The spleen was not felt. The ankles were moderately swollen. Weakness of the left side of the face and body was apparent. This, together with severe temporal headache, suggested a cerebral abscess. Coma supervened two days before death.

Laboratory Studies.—The leucocyte count varied between 3,900 and 7,200. The urine analyses and electrocardiogram were unchanged. A lumbar puncture showed 312 polymorphonuclear cells, 88 lymphocytes, and 70 erythrocytes per cubic millimeter. The concentration of total protein was 25 mg. per 100 c.c., of sugar, 74 mg. per 100 c.c., and of chloride, 721 mg. per 100 c.c. The gold sol curve was 0000121000. Cultures of three samples of spinal fluid and two samples of blood were negative. A culture from the throat and one from the ear showed no growth of pathogenic organisms. An arterial blood sample was obtained four hours before death. An electrocardiogram three hours before death was interpreted as follows: "Marked sinus arrhythmia, rate 55. In Lead III, two instances of ventricular escape are seen, with blocked P waves subsequently. The P-R interval equals 0.22 second. Marked right axis deviation. T_1 upright, T_2 inverted, and T_3 inverted. Prominent U waves."

The autopsy was performed three hours after death.

POST-MORTEM EXAMINATION

The post-mortem examination showed a markedly cyanotic, barrel-chested boy, with marked clubbing of the fingers and toes. The blood vessels of the skin were prominent, and appeared as a network of deep purple lines; indeed, all the blood vessels throughout the body were extremely prominent.

Heart.—The heart was markedly enlarged, and weighed 600 Gm. Most of the enlargement was due to the enormous hypertrophy of the right ventricle, which comprised roughly two-thirds of the total volume of the heart. The right ventricular wall measured 17 mm. in thickness. The left ventricle was relatively small, and its wall measured 14 mm. The right auricle was dilated and much more prominent than the left. The wall of the right auricle measured 2 to 3 mm. in thickness, and that of the left measured 1.5 to 2 mm. in thickness.

Fig. 1.—Exposure of right ventricle, with probe inserted through the stenotic and calcified pulmonary valve.

The congenital abnormalities were numerous. There was complete transposition of the aorta, which came directly from the right ventricle. The wall of the aorta was slightly thicker than normal, and measured 2 to 3 mm.; otherwise it was negative. The ductus arteriosus was completely closed, and there was just a dimple on the aortic intima. There was a large interauricular septal defect which measured 6 cm. in circumference. Just below the aortic valve there was a large interventricular defect which measured 5 cm. in circumference. This opened into the

left ventricular cavity just below the pulmonary valve. The pulmonary valve was bicuspid, with two well-defined commissures. The diagonal distance between the two commissures from their points of attachment on the pulmonary artery was 2.5 cm. The valve cusps were thickened, fibrous, and fused along most of this distance, except at the central portion, where an opening not more than 2 to 3 mm. in diameter was present (Fig. 1). Attached to one edge of the valve margin, undoubtedly adding to the stenosis, was a somewhat granular and calcified vegetation which measured 6 mm. in diameter and 15 mm. in length. The pulmonary artery was narrow and markedly thinned, and measured not more than 0.3 mm. in thickness. Just above the valve there was an intimal erosion about 1 cm. in diameter which was produced unquestionably by the constant irritation of the calcified vegetation. The aortic valve measured 8 cm. in circumference, and the

Fig. 2.—Exposure of the chambers of the heart, showing shortening and thickening of the chordae tendineae of the tricuspid valve.

cusps showed slight interadherence at their commissures. In addition, there were a few, pinkish-gray, firm, nodular vegetations, measuring 1 to 4 mm. in diameter, along the line of closure of the valve cusp. The tricuspid valve (Fig. 2) measured 11 cm. in circumference and showed slight, but definite, shortening and thickening of the chordae tendineae. Along the line of closure there were numerous, pale-yellow vegetations which were as large as 5 mm. in diameter. The mitral valve measured 9 cm., and was negative. The coronary arteries were patent throughout. Microscopic examination of the myocardium showed numerous small foci of fibrosis and lymphocytic infiltration, but no lesions suggestive of Aschoff nodules could be identified. The microscopic section of the tricuspid valve showed a degree of fibrosis and increased vascularity which was consistent with rheumatic infection. The pulmonary valve was too fibrotic and calcified to allow an accurate opinion regarding previous rheumatic involvement.

Lungs.—Both lungs were uniformly well aerated, and showed no evidence of consolidation. The bronchial arteries were markedly dilated and hypertrophied, and measured 4 to 5 mm. in diameter. Microscopic examination of the lungs showed no abnormality.

Kidneys.—The kidneys were tremendously hypertrophied, and, together, weighed 450 Gm. Grossly they were otherwise normal. Microscopic examination showed very severe passive venous engorgement and capillary congestion. Many of the glomeruli were normal except for congestion. Others, however, showed an increase in both endothelial cells and leucocytes which was suggestive of a grade I acute glomerular nephritis. Still others were partially or completely hyalinized. Many of the tufts showed only focal fibrosis or capsular thickening. There were no vascular changes. The changes are best interpreted as being consistent with marked passive congestion, healed embolic nephritis, and terminal acute glomerular nephritis.

Brain.—In the right temporal region of the brain there was an abscess 4 to 6 cm. in diameter, filled with a soft, gelatinous blood clot and foul-smelling gray pus. There was no overlying meningitis.

Bone Marrow.—The bone marrow was deep red in color, and showed marked hyperplasia, especially of the erythrocyte series, with replacement of the fat cells.

ANATOMIC DIAGNOSES

Congenital heart disease: Tetralogy of Fallot (hypertrophy of right ventricle, dextroposition of aorta, interauricular and interventricular septal defects, bicuspid pulmonary valve, with stenosis).

Rheumatic heart disease.

Chronic rheumatic endocarditis of the aortic, tricuspid, and (?) pulmonary valve.

Endocarditis, healed bacterial, with calcification, of the pulmonary valve.

Nephritis (healed embolic and acute glomerular, grade I).

Cerebral abscess, right temporal lobe.

Chronic passive congestion, marked, of the liver, spleen, and kidneys.

Hypertrophic pulmonary osteoarthropathy, marked.

Hyperplasia of bone marrow.

Cyanosis.

METABOLIC STUDIES

METHODS

During the first admission the patient was transferred to the research ward, and controlled studies of intake and output were made during six periods. The customary precautions were exercised. The preparation of food, collection of excreta, and the methods for analysis of the various constituents have been described.[6, 7] A preliminary period of three days was allowed for the patient to approach equilibrium on the constant diet. The diet contained 288 Gm. of carbohydrate, 38 Gm. of fat, and 61 Gm. of protein. The calculated calories amounted to 1,750. After ingestion of the diet for three days, Period 1 was begun Nov. 26, 1937. It continued for five days, was followed by a second five-day period, and then by a four-day period. Period 4 was begun Dec. 10, 1937. On that day 10 Gm. of urea were given by mouth. On the first and second day of Period 5, 8 Gm. of ammonium chloride were given orally. On the first and second day of Period 6, 20 Gm. of sodium bicarbonate were given by mouth. This period terminated after three days. All of the urine excreted was saved and partitioned into twenty-

four-hour specimens. An aliquot of each day's sample was analyzed for the various acid and base constituents. An aliquot of the diets and stools was analyzed for each period. The observations are summarized in Table I. Arterial and femoral venous blood was drawn on several occasions. Oxygen capacity, oxygen and carbon dioxide content of whole blood, and the concentration in the serum of total fixed base, sodium, potassium, calcium, chloride, bicarbonate, phosphate, and protein were ascertained (Table II). Experimental observations upon equilibrated whole blood were collected for the construction of oxygen and carbon dioxide dissociation curves.

RESULTS

The concentration of the constituents of the blood, especially oxygen and carbon dioxide, showed marked variations from normal. The oxygen capacity, 32.7 to 35.4 volumes per cent, as well as the oxygen saturation of arterial blood, 58 to 61 per cent, are critical values. Greater variations from the normal have not been reported, and most likely are incompatible with life.

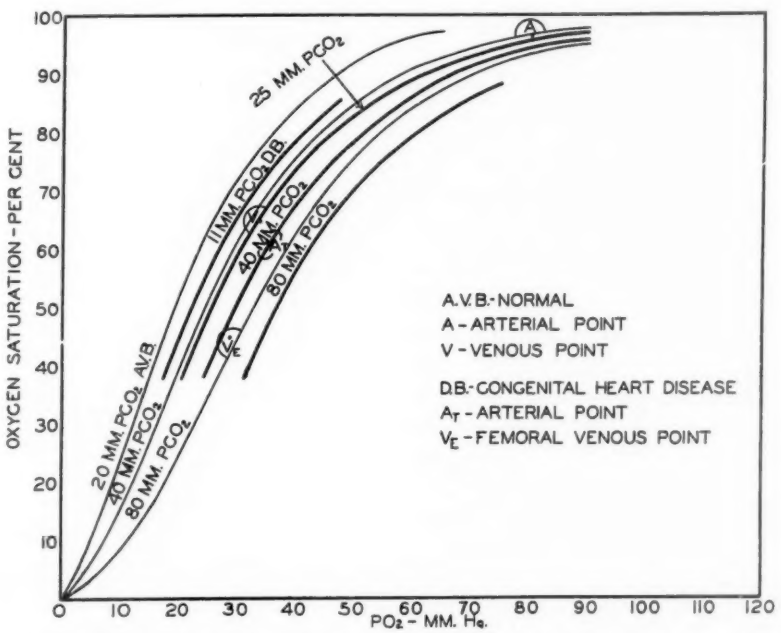

Fig. 3.—Oxygen dissociation curves of patient D. B. and normal control A. V. B.

Oxygen dissociation curves constructed at 11, 25, 40, and 80 mm. partial pressure of carbon dioxide, respectively, are given in Fig. 3. The 20, 40, and 80 mm. curves of a normal person are incorporated in the figure for comparison. The arterial (A) and venous (V) points for normals are plotted. The arterial point (A_t) for D. B. was obtained from data on samples of peripheral arterial blood. The oxygen saturation averaged approximately 62 per cent, except for the sample taken

TABLE I

SUMMARY OF CERTAIN BALANCE DATA ON D. B.

PERIOD	DATE (1937)	CONSTITUENT	DIETARY INTAKE	EXTRADIETARY INTAKE	URINARY OUTPUT	FECAL OUTPUT	DAILY BALANCE	COMMENTS
1	November 26–December 1	Sodium (m.eq.)	288	171	389	31	+ 7.8	
		Potassium (m.eq.)	275		179	57	+ 7.8	
		Calcium (m.eq.)	32		1	47	− 3.2	
		Chloride (m.eq.)	287	171	449	11	− 0.5	
		Phosphate (mg.)	3,720		2,373	1,600	− 50.	
		Nitrogen (Gm.)	50.0		44.2	4.7	+ 0.2	
2	December 1-6	Sodium (m.eq.)	277	171	433	23	− 1.6	
		Potassium (m.eq.)	255		170	51	+ 6.8	
		Calcium (m.eq.)	33		2	46	− 3.0	
		Chloride (m.eq.)	312	171	461	9	+ 2.6	
		Phosphate (mg.)	3,205		2,439	1,288	−124.	
		Nitrogen (Gm.)	48.3		44.7	5.2	− 0.3	
3	December 6-10	Sodium (m.eq.)	217	137	322	16	+ 4.0	
		Potassium (m.eq.)	199		144	36	+ 4.8	
		Calcium (m.eq.)	27		2	34	− 2.2	
		Chloride (m.eq.)	235	137	363	3	+ 1.5	
		Phosphate (mg.)	2,664		1,688	1,123	− 34.	
		Nitrogen (Gm.)	41.4		36.0	3.8	+ 0.4	
4	December 10-14	Sodium (m.eq.)	228	137	292	11	+ 15.5	10 Gm. urea, orally
		Potassium (m.eq.)	219		152	29	+ 9.5	
		Calcium (m.eq.)	25		1	22	+ 0.5	
		Chloride (m.eq.)	243	137	363	4	+ 2.8	
		Phosphate (mg.)	2,706		1,447	730	+132.	
		Nitrogen (Gm.)	38.7	4.8	39.2	2.7	+ 0.4	

TABLE I—CONT'D

PERIOD	DATE (1937)	CONSTITUENT	DIETARY INTAKE	EXTRADIETARY INTAKE	URINARY OUTPUT	FECAL OUTPUT	DAILY BALANCE	COMMENTS
5	December 14-18	Sodium (m.eq.)	231	137	423	19	− 18.5	16 Gm. ammonium chloride, orally
		Potassium (m.eq.)	226		193	52	− 4.7	
		Calcium (m.eq.)	25		1	33	− 2.5	
		Chloride (m.eq.)	249	436	608	10	+ 16.8	
		Phosphate (mg.)	2,912		1,926	1,043	− 14.	
		Nitrogen (Gm.)	43.1	4.1	40.7	4.4	+ 0.5	
6	December 18-21	Sodium (m.eq.)	168	579	257	34	+152.0	40 Gm. sodium bicarbonate, orally
		Potassium (m.eq.)	164		77	40	+ 15.7	
		Calcium (m.eq.)	18		1	35	− 6.0	
		Chloride (m.eq.)	173	103	215	8	+ 15.6	
		Phosphate (mg.)	2,202		855	1,292	+ 15.	
		Nitrogen (Gm.)	30.8		29.5	5.0	− 1.2	

just before death. The venous (V_e) point was obtained from analysis of femoral venous blood.

The cell volume was the greatest that we have observed in any pathologic state. The cell volume was 85 per cent or more, except for a short time after the withdrawal of large amounts of blood for chemical studies. The erythrocytes were but slightly hypochromic,[8] and contained almost a normal concentration of hemoglobin.

There was a profound acidosis. The carbon dioxide content of the serum was reduced about 8 m.M. per liter (18 volumes per cent) below the average normal. The pH_s was less than 7.30. The ingestion of 16 Gm. of ammonium chloride accentuated the acidosis, whereas the ingestion of 40 Gm. of sodium bicarbonate increased the carbon dioxide content of whole blood above normal and restored the pH_s to normal. The content of bases and the other acid constituents in the serum was ascertained, and, except for potassium and phosphate, there was no significant deviation from the normal. The concentration of potassium was as high as 7.4 m.eq. per liter, and of phosphate, 2.2 m.eq. per liter. Since the nonprotein nitrogen varied from 45 to 54 mg. per 100 c.c., it was assumed that the phosphate elevation, also, was associated with renal insufficiency.

TABLE II

OBSERVATIONS ON ARTERIAL AND VENOUS BLOOD OF D. B.

DATE	SOURCE	WHOLE BLOOD				TRUE PLASMA OR SERUM										ARTERIAL pCO_2 (MM. Hg.)	ALVEOLAR pCO_2 (MM. Hg.)	PERIPHERAL ARTERIAL pH	PULMONARY VENOUS pH*	COMMENTS
		OXYGEN CAPACITY (VOL. PER CENT)	OXYGEN SATURATION (PER CENT)	CELL VOLUME (PER CENT)	TOTAL CARBON DIOXIDE (M.M. PER LITER)	TOTAL FIXED BASE (M.EQ. PER LITER)	SODIUM (M.EQ. PER LITER)	POTASSIUM (M.EQ. PER LITER)	CALCIUM (M.EQ. PER LITER)	TOTAL CARBON DIOXIDE (M.M. PER LITER)	CHLORIDE (M.EQ. PER LITER)	PHOSPHATE (M.EQ. PER LITER)	PROTEIN (GM. PER 100 C.C.)	NONPROTEIN NITROGEN (MG. PER 100 C.C.)	URATE (MG. PER 100 C.C.)					
Nov. 9, 1937	Brachial artery	35.4	61	86.8	13.9	156.8	135.0			16.7	106.5		5.6			38	25	7.25	7.45	
Nov. 19, 1937	Brachial artery	35.3	61	85.6	13.9	153.1	140.3			17.7	106.9		6.0			37		7.28	7.47	
Nov. 19, 1937	Femoral vein	34.2	48	84.6	15.9															
Nov. 22, 1937	Brachial artery	34.8	69		14.5															After 40 hours of breathing a 50 per cent oxygen mixture
Nov. 22, 1937	Femoral vein	34.6	44		17.5															
Dec. 10, 1937	Femoral artery	35.0				149.0	135.9	6.3	4.5	20.2	105.6	1.7	5.6	49	11.9					
Dec. 14, 1937	Femoral artery	34.1		84.3		150.8	136.0	5.1		21.6	104.9	2.2	5.6	43	13.5					10 Gm. of urea taken orally on Dec. 10, 1937
Dec. 16, 1937	Femoral artery	33.5		81.8	11.2	148.9	132.7	7.4		13.8	113.7	1.6	6.0	49	11.1	36	18	7.19	7.51	16 Gm. of ammonium chloride taken orally during 48 hours previous to withdrawal of blood
Dec. 20, 1937	Femoral artery	32.7		77.1	22.7	157.5	141.5	5.4	4.2	31.9	101.0	1.4	5.2	42	8.6	52	34	7.41	7.60	40 Gm. of sodium bicarbonate taken orally during 48 hours previous to withdrawal of blood
Feb. 2, 1938	Anticubital vein	34.6		85.5									5.6	54						
Nov. 19, 1938	Femoral artery	33.3	58	85.0						17.4										

*Calculated from alveolar pCO_2 and the carbon dioxide dissociation curves. It was assumed that the pulmonary venous blood was 95 per cent saturated with oxygen.

The urinary excretion of ammonia and titratable acid, and its pH, were remarkably constant. In the first four periods the daily ammonia production ranged from 23 to 29 m.eq. It was little affected by the ingestion of 8 Gm. of urea. After ammonium chloride ingestion, it increased to a maximum of 59 m.eq. Following the ingestion of sodium bicarbonate, it decreased to 9.8 m.eq. The titratable acid and hydrogen-ion concentration showed little variation except after sodium bicarbonate ingestion. There was a slight negative calcium balance in most periods (Table I). This has been the usual finding in our experience with patients on a constant metabolic regime, especially those whose activity is restricted. The patient was in nitrogen and phosphate balance throughout the study. A positive potassium balance was noted in all periods except Period 5. Presumably, this was associated with the elevated potassium in the serum. After the ingestion of urea and sodium bicarbonate there was a significant retention of sodium. A negative balance followed ammonium chloride ingestion. The patient was in positive chloride balance in Periods 5 and 6. Equilibrium was established in the other periods.

DISCUSSION

The history and physical signs made a diagnosis of congenital heart disease in our case quite certain. It was predicted that the anatomic defects would be similar to those characterized as the tetralogy of Fallot.[9] This was confirmed at post-mortem examination, at which the following cardiac abnormalities were evident: hypertrophy of the right ventricle, dextroposition of the aorta, pulmonary stenosis, and an interventricular septal defect. There was, in addition, an interauricular septal defect. The age at which the patient died is above the average but does not approach the longevity reported elsewhere. Many patients with the tetralogy of Fallot die before adolescence, but some live to the third and fourth decade; the record to date is fifty-nine years and eight months,[10] but one of us (P. D. W.) has under observation at present a woman, 66 years of age, with undoubted clinical evidence of the disease, who is still in fair health; evidently it is a mild case.

It is of interest to trace briefly the history of the recognition of the congenital cardiac anomaly now widely known as the tetralogy of Fallot. Fallot, in 1888, did not pretend that he was the first to describe the anomaly, but he did a service to medicine by pointing out that at least three-quarters of all persons who show cyanosis and clubbing of the fingers from infancy do have this tetralogy of defects. Thus, without further ado or study, the chances are at least 3 to 1 that such persons have the anomaly; physical examination (showing little evident cardiac enlargement and only a pulmonary systolic murmur), the electrocardiogram (with its high degree of right axis deviation and normal rhythm),

and the roentgenographic contour of the heart (more or less sabot-shaped, with prominent aorta and small pulmonary arterial tree) confirm the diagnosis.

As one consults early medical literature, one finds more and more case reports, autopsies, in the main, of what has since been called the tetralogy of Fallot. We have found no reference to this syndrome, however, before the eighteenth century. Bonetus[11] did not describe such a case in his Sepulchretum, in 1679, nor did Mangetus[12] in the second edition of the Sepulchretum, in 1700. In the eighteenth century there was the report by Morgagni[13] of a case of pulmonary stenosis in a girl, aged 16 years, who had been cyanotic since birth. The right ventricle and right auricle were very large, and there was said to be a patent foramen ovale. Sandifort,[14] in 1777, reported similar abnormalities in a boy who died at the age of 12 years. Early in the nineteenth century the physiologic disturbances associated with congenital heart disease were presented ably by Farre.[15] He reported several cases of cyanosis and clubbed fingers in which the tetralogy was demonstrated at post-mortem examination. Gintrac,[16] in 1824, and Peacock,[17] in 1858, described additional cases. It was not until 1888 that Fallot's[9] description was published, and this dates the eponym.

Our patient was a semi-invalid during the last year of his life. He refused, however, to be considered as one. He was above the average scholastically and, in spite of the physical handicap, made a commendable record at his studies. On physical examination, the clubbing of the fingers was striking. It was largely soft tissue hypertrophy, however, as no tufting of the terminal phalanges was evident roentgenologically. The external ears were paper-thin and prominent. The pigmentation of the skin of the extremities, which has been observed in other patients with morbus caeruleus,[18, 19] as well as in patients suffering from chronic mountain sickness,[5] presumably is associated with anoxemia and peripheral venous stasis.

It was believed, from the clinical evidence, that the patient had experienced attacks of acute rheumatic fever between the ages of 10 and 12, as well as subacute bacterial endocarditis while under observation eight or nine months before death. The presumptive diagnosis of subacute bacterial endocarditis was based upon the presence of fever, hematuria, failing cardiac reserve, pleural pain, with a friction rub, and abdominal cramps (? embolic). If bacterial endocarditis develops in a case of congenital heart disease, usually it is a terminal,[20] rather than an intercurrent, event. Our patient was not treated with any specific drug, such as a sulfonamide derivative, or with any immune vaccine or serum. Nevertheless, the calcified vegetations discovered at the post-mortem examination strongly supported the clinical observation that he had recovered from an endocarditis. It has been stated previously that several blood cultures showed no growth. The failure to cultivate from

the blood and identify a pathogenic organism is evidence against, but does not rule out, the diagnosis of subacute bacterial endocarditis, especially in congenital heart disease. In fact, it may be extremely difficult to isolate the organism in subacute bacterial endocarditis which is superimposed upon a congenitally deformed heart.[21] Since rheumatic lesions, as well as those of subacute bacterial endocarditis, may calcify, the question of which malady was responsible must be answered by the pathologic studies. These offer conclusive evidence that the patient suffered first from rheumatic heart disease and later from subacute bacterial endocarditis and that the bacterial endocarditis increased the stenosis of the already congenitally stenosed pulmonary valve.

One observation of obscure significance during life was the constant, well-marked, early diastolic murmur at the base of the heart, which was interpreted as due to aortic regurgitation, despite a normal pulse pressure. We did not know whether this aortic regurgitation was to be ascribed to a complicating rheumatic aortic valve disease, or to dilatation of the aortic ring simply as the result of the markedly increased aortic output. It turned out that the latter was the correct explanation; we have encountered it in one other case of the tetralogy of Fallot.

Death was precipitated by a cerebral abscess. Although the cardiac reserve was strained to the breaking point, death was not caused by cardiac failure, per se. Just as the blood appeared to be sterile during what we deem was an attack of endocarditis, so was it sterile when a diagnosis of cerebral abscess was apparent, and, at autopsy, no growth was seen in a culture of the blood from the chambers of the heart. A culture from the cerebral abscess alone showed pathogenic organisms. These were colon bacilli and Gram-positive cocci in clusters. The incidence of cerebral abscess in patients with a sizable septal defect is believed by Abbott to be more than coincidence.[22] Rabinowitz and his associates[23] were willing to go so far as to state that "the presence of an idiopathic brain abscess should lead one to suspect the possibility of the presence of a congenital cardiac defect."

The concentration of the gases in the blood and the results of the metabolic studies were as interesting as the clinical and pathologic observations. It is believed by us that the concentration of the gaseous constituents of the arterial blood approached the extreme limit of variation from the normal, beyond which life cannot be maintained. In spite of the deviations from normal, the body had made a remarkably adequate adjustment, and death was caused by an infection in the brain, not directly from inadequate oxygen transport or recurring cardiac failure.

The cell volume varied from 82 to 87 per cent, and the oxygen capacity, from 32.7 to 35.4 vol. per cent. The concentration of hemoglobin in the whole blood increased the density to such an extent that the blood

seemed almost to congeal in the veins. The blood was so viscous that, during an arterial or venous puncture, the plunger of an oiled syringe had to be withdrawn forcefully in order to introduce blood into the barrel. The viscosity of the blood offered considerable peripheral resistance and imposed a real burden upon the myocardium.

The oxygen saturation of the arterial blood varied between 62 and 58 per cent. The former value was obtained when the patient was ambulatory; the latter was obtained only a few hours before death. Approximately a year elapsed between the two observations. Very few studies of the oxygen saturation of the arterial blood of patients with congenital heart disease have been reported since Van Slyke's development of the manometric blood gas analyzers made them possible. To the twenty cases reported in the literature we have added five of our own, and summarized the pertinent data in Table III. Certain data, only, on patients M. G., E. R., H. W., and D. S., who were seen by us, are included in the table. Other observations made upon these patients will be described in detail elsewhere.

It is apparent that, when the arterial oxygen saturation approaches 60 per cent, oxygen transport, even at rest, becomes a critical problem, and life cannot long be maintained. A similar conclusion was reached in our studies in the Chilean Andes. The lowest saturation in a permanent resident at 17,500 feet was 67 per cent.[5] At 20,100 feet the oxygen saturation of the arterial blood of a temporary resident was 55 per cent.[24] Both observations were made on persons who were healthy and physically sound. The permanent residents at 17,500 feet admitted no symptoms except dyspnea on exertion. The temporary resident had no distressing symptoms while living at 17,500 feet, but complained bitterly of headache, anorexia, and fatigue after living at 20,100 feet for twenty-four hours with an oxygen saturation of 55 per cent. The subject remained ambulatory in spite of these symptoms and an uncomfortably low environmental temperature. It is noteworthy that patients with morbus caeruleus may remain ambulatory with an improperly functioning heart and a blood oxygen saturation which corresponds to that at an altitude of approximately 4 miles. Of course, many patients with congenital heart disease become adjusted to a progressive diminution in the partial pressure of oxygen in the blood over a long period of time, just as residents at high altitudes become adjusted.

These studies cast considerable doubt upon the assumption that the symptoms which are sometimes attributed to chronic carbon monoxide poisoning[25] are produced by recurrent anoxemia, per se. It cannot be denied that repeated exposure to small amounts of carbon monoxide may produce a syndrome that is recognized as carbon monoxide poisoning. The symptoms, however, should be attributed to some factor or factors in addition to mild anoxemia. The observations of Asmussen and Chiodi,

TABLE III

TABLE III

OBSERVATIONS ON BLOOD GAS CONCENTRATIONS IN PATIENTS WITH CONGENITAL HEART DISEASE, AS REPORTED IN THE LITERATURE

AUTHORS	CASE	AGE (YEARS)	SEX	PULMONARY VENTILATION (LITERS PER MINUTE)	ARTERIAL BLOOD			ARTERIAL pH_a	ALVEOLAR pCO_2 (MM. HG.)	COMMENTS
					OXYGEN CAPACITY (VOLUMES PER CENT)	OXYGEN SATURATION (PER CENT)	CARBON DIOXIDE CONTENT (VOLUMES PER CENT)			
Normal mean					21.0	95	48	7.40	40	
Campbell, et al.[42]	No. 15	20	♂	9	24.7	69	36.9	7.31	24	Patent septum, pulmonary stenosis
	No. 17	35	♂	6	27.9	77	39.6	7.32	25	Patent septum, pulmonary stenosis
	No. 43	24	♂		31.5	84	35	7.30		Patent septum, pulmonary stenosis
Raab, et al.[19]		15	♂		31.6	75				Tetralogy of Fallot
Henderson[1]					34.0	76	38.5	7.27	36	Tetralogy of Fallot
Mainzer[35]		25			25.3	66	37.0	7.44		Roger's disease
D'Autrebande, et al.[43]	No. 1	12	♂	5	32.3	63*	28*	7.37	23	Patent septum, pulmonary stenosis
	No. 2	13	♀	5	27.2	70*	33.6*	7.40	25	Cyanosis only on exertion
	No. 3	19	♂	13	29.8	81*	34.3*	7.37	27	
Hitzenberger and Tuckfeld[39]		26	♂	15	35.2	62	27.5	7.17	26	Patent septum, transposition of great vessels
Richards, et al.[28]	A. S.	12	♀	9	33.8	60	38.6		23	Tetralogy of Fallot
Segall[41]	I. M.	23	♂		26.3	64				Tetralogy of Fallot
Meyer[34]		22	♂	17	35.0	82	35.0	7.47	29	Patent septum, pulmonary stenosis
Uhlenbruck[44]	M. S.	3	♀		31.9	88	35	7.38	23	Tetralogy of Fallot
Schoen and Derra[45]	No. 1	23	♂		18.4	82	42.0			Patent septum
	No. 2	15	♀		19.9	75	41.4		29	Patent septum
	No. 3	21	♂		29.8	72	47.3			Patent septum
	No. 4	21	♂		30.8	56	32.7		28	Pulmonary stenosis
Mayer and Israel[46]	M. L.	24	♀	6	17.9	69	46.7			Tetralogy of Fallot
Pijoan and Bérard[47]		23	♀		23.0	78				Tetralogy of Fallot
Talbott, et al.	D. B.	19	♂		35.4	61	31.1	7.25	25	Tetralogy of Fallot
	M. G.	35	♀		32.2	60	32.9	7.30		No anatomic diagnosis made. Morbus caeruleus
	E. R.	27	♂		31.5	84	36.6			No anatomic diagnosis made. Morbus caeruleus
	H. W.	21	♀		28.1	79	38.2	7.34		Probably tetralogy of Fallot
	D. S.	38	♂		24.1	84	38.6	7.38		No anatomic diagnosis made. Morbus caeruleus

*Observations reported by authors to be unreliable.

recently reported,[26] support this contention. These investigators studied oxygen deficiency in normal human subjects by two different procedures: (1) by replacing a part of the oxyhemoglobin with carbon monoxide hemoglobin, and (2) by allowing the subject to breathe a gas mixture which was low in oxygen. Anoxemia produced by partial carbon monoxide poisoning elicited little or no respiratory response and had little or no effect upon cardiac output. On the other hand, a diminished partial pressure of oxygen in the inspired air produced pronounced hyperventilation and an increase in cardiac output.

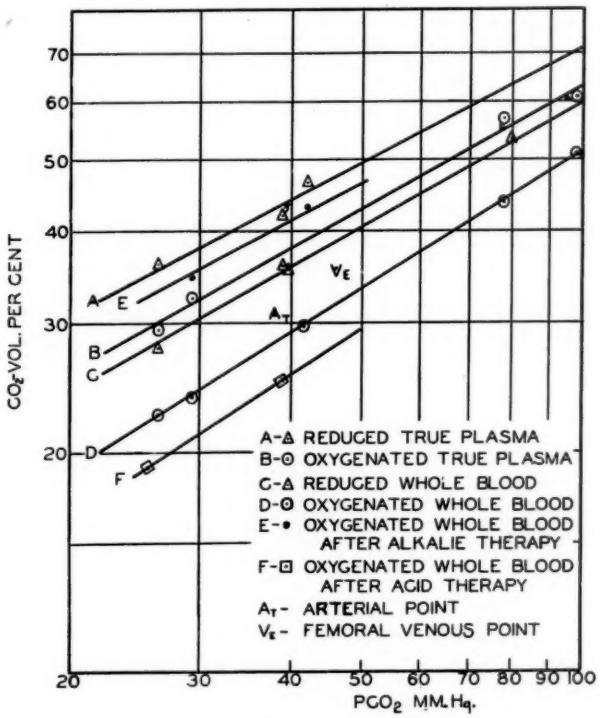

Fig. 4.—Carbon dioxide dissociation curves of patient D. B. plotted on logarithm paper.

Our patient with congenital heart disease was placed in an oxygen tent and allowed to breath for forty hours a gas mixture which contained 50 per cent oxygen. No marked increase in the oxygen saturation of the arterial blood followed this treatment, and only slight symptomatic improvement was admitted. Hemsath, et al.,[27] and Richards, et al.,[28] have reported similar results. It is concluded that oxygen therapy is ineffective in increasing the transport of oxygen to the tissues of patients with a right-to-left heart shunt. The explanation is readily apparent. Oxygen therapy increased the partial pressure of oxygen only in the pulmonary circuit. In morbus caeruleus the arterial blood is saturated about as completely in these vessels as it is normally, even

though the saturation in the peripheral arteries is reduced considerably. Since oxygen therapy does not alter the arteriovenous shunt, it cannot be expected to increase the supply of oxygen to the tissues.

Femoral venous blood was investigated on two occasions. At the first observation the saturation of oxygen was 48 per cent, or approximately 20 per cent below normal. It decreased to 44 per cent following prolonged oxygen inhalation. This change is not significant.

There is some theoretical basis for the assumption that there may be a direct correlation between unsaturation of blood and increase in oxygen capacity in healthy persons. The Andean studies[24] showed that this assumption was a good approximation. The data on congenital heart disease are more discordant. The association of a serious disease with anoxemia is probably responsible for the wide scattering.

It would be interesting and might be clinically important if information were available concerning the amount of blood that passes through the cardiac shunt. An earnest, but unsuccessful, attempt was made to measure the cardiac output with the acetylene method. We were forced to rely, therefore, upon the formula described by Lundsgaard and Van Slyke,[29] which is approximate and not precise. The application of our data to the formula indicated that nearly three-fourths of the blood which circulated through the heart was not aerated in the lungs.

Changes in the carbon dioxide content of the arterial blood are as characteristic of morbus caeruleus as are changes in oxygen content. When the malady is advanced and the diagnosis is obvious clinically, there are a diminished content of carbon dioxide in the blood, a diminution in the height of the carbon dioxide dissociation curve (Fig. 4), and a decrease in the partial pressure of alveolar carbon dioxide.[30-32] Abbott,[22] with the collaboration of Boothby, was the first to consider theoretically the variation in carbon dioxide during the respiratory cycle in congenital heart disease. In 1912 they postulated an increase above normal in the difference in carbon dioxide content of arterial and venous blood. The difference is approximately 4 volumes per cent[33] in healthy persons, whereas, in the case of D. B., it was nearly 9 volumes per cent. The total carbon dioxide content of the arterial blood was markedly reduced. The average range for normal persons is from 46 to 54 per cent. We have chosen 48 as a mean value. One of the lowest values for any patient with congenital heart disease listed in Table III was observed in the case of D. B. This was 31.1 volumes per cent. Few exceeded 40 volumes per cent. The partial pressure of carbon dioxide in the alveolar air showed a similar decrease. The average value for normals is approximately 40 mm. Hg. It is usually below 30 mm. in patients with advanced morbus caeruleus.

Finally, variations in the hydrogen-ion concentration may be calculated from the carbon dioxide data. It is the custom when studying trained

subjects without a cardiac or a pulmonary defect to make the calculation for pH_s from the observations on alveolar pCO_2 and the carbon dioxide content of arterial blood.[33] An alternate procedure is to construct a set of carbon dioxide dissociation curves, ascertain the carbon dioxide content of arterial blood, and locate the arterial point on the constructed graph. The calculated pH_s should be the same by either method. If the pH_s of arterial blood is desired in cases of morbus caeruleus, the second procedure must be employed. The alveolar pCO_2 cannot be utilized because it does not represent the partial pressure of carbon dioxide in the peripheral arterial blood, but only that of arterialized blood in the pulmonary circuit. All of the pH_s values given in Table III, except that of Meyer,[34] were obtained by this procedure. Except for this observation and that of Mainzer,[35] all of the values for pH_s are 7.40 or less. The lowest was 7.25, in our case (D. B.).

It is apparent that the blood gas concentrations in patients with morbus caeruleus deviate consistently from the normal, and this, we believe, is characteristic. They include an increased oxygen capacity, a decreased oxygen saturation and a decreased carbon dioxide content of arterial blood, a decreased partial pressure of alveolar pCO_2, and a decreased arterial pH_s.

The pathogenesis of the unsaturation of arterial blood is most likely mechanical. Unsaturated venous blood from the right side of the heart is shunted through the septal defect or into the aorta, and thence into the peripheral circulation without passing through the lungs. The physiologic and pathologic effects cannot be altered as long as the anatomic defects persist. A progressive increase in the oxygen capacity follows the prolonged anoxemia. The mechanism of the increase is probably similar to that observed in dwellers at high altitudes. The pathogenesis of the variation from normal in carbon dioxide content and pH_s is more difficult to ascertain.

The lowering of the carbon dioxide content of the blood and the decreased partial pressure of alveolar carbon dioxide have been attributed to hyperventilation. Such a phenomenon may contribute, but it is not solely responsible. Uncomplicated hyperventilation does not produce acidosis, as is observed in congenital heart disease, but alkalosis.[36] Furthermore, only a portion of the blood which enters the peripheral arterial system traverses the pulmonary circuit and is available for exposure to hyperventilation. Nor is anoxemia mainly responsible for the changes in carbon dioxide. The profound anoxemia at high altitudes[24] is associated with parallel decreases in alveolar pCO_2 and the carbon dioxide content of arterial blood. The ratio of free to combined carbon dioxide tends to remain constant, so that the pH_s shows little variation from normal. Thus, neither hyperventilation nor anoxemia is responsible for an uncompensated acidosis.

An increased concentration of acid in the blood could account for all of the variations. No adequate study of the acid-base balance of the blood of patients with congenital heart disease has ever been reported. Our observations (Table II) are comprehensive and instructive. The concentrations of the individual bases show a slight decrease in serum sodium and a slight increase in serum potassium. The sum of the bases, however, although it is at the lower border of normal, is not below normal. A deficiency of base, therefore, cannot be held responsible for the acidosis and diminished alkaline reserve. The acid side of the balance column should be reviewed next. Complete acid-base data for Dec. 10, 1937, are assembled in Table IV. The concentrations of all of the constituents are expressed in milliequivalents per liter. In this sample of serum the concentrations of chloride and phosphate were normal, whereas that of proteinate was a low normal. The concentration of bicarbonate was reduced about 10 m.M. per liter; this amount had been replaced by an equivalent amount of undetermined acid. This sample of blood does not represent the extreme, for other samples from D. B. showed even greater amounts of undetermined acids. The nature of the undetermined acid is not known. Ketone bodies were not present in any routine urine specimen that was examined. The content of lactic acid was not ascertained, but it is unlikely that this acid accounted in large part for the undetermined excess. Increased production of organic acids, as well as diminished renal excretion of these and normally appearing acids, was probably operative. The evidence in favor of an increased production of organic acids is indirect. In other conditions associated with renal failure, such as bichloride of mercury poisoning,[37] an increased production of organic acid has been assumed.

TABLE IV

ACID-BASE CONSTITUENTS OF THE SERUM ON DEC. 10, 1937

(Concentrations are expressed in milliequivalents per liter.)

BASES		ACIDS	
Sodium	135.9	Chloride	105.6
Potassium	6.3	Bicarbonate	18.2
Calcium	4.5	Proteinate	12.8
Magnesium	1.5*	Phosphate	1.7
Total fixed base	148.2		138.3

*Assumed.

Study of renal function and quantitative estimation of renal insufficiency in patients with congenital heart disease has not been pursued intensively by many investigators. Mainzer,[35] Irvine-Jones,[38] Hitzenberger and Tuckfeld,[39] Leadingham,[40] and Segall[41] are the only authors that we have discovered who have referred to the subject. In a survey of 100 cases of congenital heart disease, Irvine-Jones noted that albuminuria had been reported in thirteen. Few showed cylinduria. It

was apparent to him that the presence of albuminuria was associated with a rapidly fatal outcome. Albuminuria, erythrocytes, and casts were noted in the urine of the patient reported by Segall. At autopsy the kidneys showed parenchymatous degeneration, but no evidence of nephritis. Similar clinical observations were made in Mainzer's case, but no autopsy findings were reported. Hitzenberger and Tuckfeld[39] noted large amounts of albumin and many erythrocytes and leucocytes in the urine of the patient described by them. The blood pressure was 140/115. Since the patient was only 26 years of age, the elevation of the diastolic pressure, together with the urinary abnormalities, points toward severe renal damage. The concentrations of the gas constituents in the blood were similar to those in our case.

Evidence of renal insufficiency in our patient was striking and persistent. The concentration of nonprotein nitrogen in the serum varied between 42 and 54 mg. per 100 c.c. during the year before death. The maximum specific gravity during two urine concentration tests was only 1.018. The ability to excrete phenolsulphonphthalein was impaired likewise. In the first twenty-five minutes after the intravenous injection of the dye, only 20 per cent was excreted, or 0.8 per cent per minute. A normal person should excrete 1.7 c.c. per minute during the first fifteen-minute period. Finally, intravenous pyelography showed poor excretion of diodrast.

The intake and output studies furnished additional evidence that the kidneys functioned poorly and were unable to participate effectively in regulating the acid-base balance of the blood. The pH and titratable acid of the urine were fixed except during the period of sodium bicarbonate ingestion. It is significant that the ingestion of ammonium chloride had little effect upon the urinary pH. It is believed that the above-mentioned values were constant because of a decrease in ability to form ammonia. Ammonia excretion was increased above the fixed daily amount only after the ingestion of ammonium chloride. Even these variations were not great. It is possible that the kidneys had become intolerant to the persistent acidosis and were less labile in the formation of ammonia than formerly. A complicating and equally important factor in the pathogenesis of the renal insufficiency was anoxemia. It is presumed by us that anoxemia may produce disturbances in kidney function without underlying, demonstrable, morphologic changes. At least it can be stated that at autopsy no anatomic changes were observed in the kidneys which could explain all of the above-mentioned findings.

It is regrettable that the clearance rates of inulin and creatinine were not ascertained in the case of D. B. These observations were collected on E. R., however, and the results are probably applicable. E. R. had morbus caeruleus, but was less handicapped than D. B. The clinical evidence of renal insufficiency was similar. The inulin clearance of the

plasma in the case of E. R. was 65 c.c. per minute, and, of creatinine, 83 c.c. per minute. The normal values are 100 c.c. and 140 c.c., respectively. It is to be hoped that further observations on renal function in cases of morbus caeruleus will be made in the future.

SUMMARY

Clinical, metabolic, and pathologic studies of a patient with advanced morbus caeruleus (tetralogy of Fallot) are reported. The patient died at the age of 19, and had been cyanosed since the age of 2. He was proficient scholastically, and, until a year before death, suffered a minimum of handicap from his malady. He was thought to have had rheumatic fever at the age of 9 and subacute bacterial endocarditis during his last year of life. A colon bacillus abscess of the cerebrum was immediately responsible for death.

The metabolic investigations revealed a profound variation from the normal in the acid-base equilibrium of the body, and changes in renal function. As much as 75 per cent of the blood in the cardiac chambers was thought to traverse a right-to-left shunt. The oxygen saturation of the arterial blood varied between 62 and 58 per cent. These are critical levels for human existence. The oxygen capacity was about 35 volumes per cent. The carbon dioxide content of the arterial blood was less than 33 volumes per cent. The arterial pH_s was less than 7.29. A profound, uncompensated acidosis was attributed to the increased concentration of undetermined acids and failure of the respiratory center to maintain the usual balance between free and combined carbon dioxide. The functional insufficiency of the kidneys was attributed to anoxemia, venous congestion, and acidosis.

REFERENCES

1. Henderson, L. J.: Sur l'application de la méthode nomographique à l'étude des phénoménes respiratoires dans le sang, Compt. rend. Acad. d. sc. **180**: 2066, 1925.
2. Bock, A. V., Dill, D. B., Edwards, H. T., Henderson, L. J., and Talbott, J. H.: On the Partial Pressures of Oxygen and Carbon Dioxide in Arterial Blood and Alveolar Air, J. Physiol. **68**: 277, 1929.
3. Dill, D. B., Edwards, H. T., Folling, A., Oberg, S. A., Pappenheimer, A. M., Jr., and Talbott, J. H.: Adaptations of the Organism to Changes in Oxygen Pressure, J. Physiol. **71**: 47, 1931.
4. Talbott, J. H.: Studies at High Altitudes. II. Morphology and Oxygen Combining Capacity of the Blood, Folia haemat. **55**: 23, 1936.
5. Talbott, J. H., and Dill, D. B.: Clinical Observations at High Altitude. Observations on Six Healthy Persons Living at 17,500 Feet and a Report of One Case of Chronic Mountain Sickness, Am. J. M. Sc. **192**: 626, 1936.
6. Talbott, J. H., Jacobson, B. M., and Oberg, S. A.: The Electrolyte Balance in Acute Gout, J. Clin. Investigation **14**: 411, 1935.
7. Talbott, J. H.: Interpretation of Clinical Chemical Procedures, Ohio State M. J. **35**: 137, 1939.
8. Weber, F. P.: Polycythaemia Anaemia Secondary to Congenital Cardiac Septal Defect, in Association With an Anaemia-Producing Agent, Proc. Roy. Soc. Med. **25**: 789, 1932.
9. Fallot, A.: Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque), Marseille méd. **25**: 77, 138, 207, 270, 341, 403, 1888.

10. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot. Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, J. A. M. A. **92**: 787, 1929.
11. Bonetus, T.: Sepulchretum sive Anatomia Practica, ex Cadaveribus Morbo denatis, Geneva, 1679.
12. Mangetus, J. J.: Theopili Boneti, Sepulchretum, ed. 2, Geneva, 1700.
13. Morgagni, G. B.: De Sedibus, et Causis Morborum per anatomen indigatis, libri quinque, Venice, 1761.
14. Sandifort, E.: De rarissmo cordis vitio, Obs. Anat. Pathol., Luguni Batavorum, 1777.
15. Farre, J. R.: Pathological Researches. Essay I. On Malformations of the Human Heart, Illustrated by Numerous Cases, London, 1814.
16. Gintrac, E.: Observations et recherches sur la cyanose, ou maladie bleue, Paris, 1824.
17. Peacock, T. B.: Cases of Malformation of the Heart, London, 1864.
18. Volini, I. F., and Flaxman, N.: Tetralogy of Fallot. Report of a Case in a Man Who Lived to His Forty-First Year, J. A. M. A. **111**: 2000, 1938.
19. Raab, W., Weiss, R., Löwbeer, B., and Rihl, J.: Untersuchungen über einen Fall von kongenitalem Herzvitium, Wien. Arch. f. inn. Med. **7**: 367, 1923.
20. Harrison, W. F.: Congenital Heart Disease, Extreme Congenital Pulmonary Stenosis (Tetralogy of Fallot); Collateral Pulmonary Circulation; Massive Right-Sided Vegetative Endocarditis, AM. HEART J. **5**: 213, 1929.
21. White, P. D., Boyes, J. H.: Subacute Bacterial (*Streptococcus Viridans*) Endocarditis and Endarteritis Involving the Tricuspid Valve and the Pulmonary Artery in a Unique Case of the Tetralogy of Fallot Complicated by Congenital Pulmonary Regurgitation, AM. HEART J. **7**: 802, 1932.
22. Abbott, M.: Congenital Heart Disease, Nelson's Loose Leaf Medicine, **4**: 207, 1932.
23. Rabinowitz, M. A., Weinstein, J., and Marcus, I. J.: Brain Abscess (Paradoxical) in Congenital Heart Disease, AM. HEART J. **7**: 790, 1932.
24. Dill, D. B., Christensen, E. H., and Edwards, H. T.: Gas Equilibria in the Lungs at High Altitudes, Am. J. Physiol. **115**: 530, 1936.
25. Beck, H. G.: The Clinical Manifestations of Chronic Carbon Monoxide Poisoning, Ann. Clin. Med. **5**: 1088, 1927.
26. Asmussen, E., and Chiodi, H.: The Effect of Hypoxemia on Ventilation and Circulation in Man, Am. J. Physiol. **132**: 426, 1941.
27. Hemsath, F. H., Greenberg, M., and Shain, J. H.: Congenital Cardiac Anomalies in Infants. Report of Five Cases—(1) Accessory Ventricle, (2) Tetralogy of Fallot With Right Aortic Arch and Redundant Left Ductus Arteriosus, (3) Tetralogy of Fallot With Anomalous Band in Right Auricle, (4) Complete Transposition of Arterial Trunks, and (5) Double Defect of Ventricular Septum, Am. J. Dis. Child. **51**: 1356, 1936.
28. Richards, D. W., Jr., Riley, C. B., and Hiscock, M.: Congenital Heart Disease. Measurements of the Circulation, Arch. Int. Med. **47**: 484, 1931.
29. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, Medicine **2**: 1, 1923.
30. FitzGerald, M. P.: The Alveolar Carbonic Acid Pressure in Diseases of the Blood and in Diseases of the Respiratory and Circulatory Systems, J. Path. & Bact. **14**: 328, 1910.
31. Straub, H., and Meier, K.: Blutgasanalysen, Deutsches Arch. f. klin. Med. **129**: 54, 1919.
32. Govaerts, P., and Lequime, J.: La teneur du sang du coeur droit en acide carbonique dans la communication interventriculaire pure, Nederl. tijdschr. v. geneesk. **81**: 260, 1937.
33. Henderson, L. J.: Blood. A Study in General Physiology, New Haven, 1928, Yale Univ. Press.
34. Meyer, P.: Hämodynamik und Hämophysikochemie bei einem Fall von Ventrikelseptumdefekt mit Pulmonalstenose, Ztschr. f. klin. Med. **120**: 341, 1932.
35. Mainzer, F.: Analyse eines kongenitalen Herzfehlers (Zugleich ein Beitrag zur Bedeutung der Hämoglobinvermehrung bei Sauerstoffmangel), Ztschr. f. klin. Med. **108**: 489, 1928.
36. Talbott, J. H., Cobb, S., Coombs, F. S., Cohen, M. S., and Consolazio, W. V.: Acid-Base Balance of the Blood in a Patient With Hysterical Hyperventilation, Arch. Neurol. & Psychiat. **39**: 973, 1938.
37. Talbott, J. H., Coombs, F. S., and Consolazio, W. V.: Electrolyte Balance During Recovery From Mercury Bichloride Poisoning, Arch. Int. Med. **60**: 301, 1937.

38. Irvine-Jones, E. I. M.: A Clinical Study of Congenital Heart Disease in Childhood, AM. HEART J. **2**: 121, 1926.
39. Hitzenberger, K., and Tuckfeld, F.: Physikalisch-Chemische Verhältnisse des Blutes bei symptomatischer Polyglobulie, Ztschr. f. klin. Med. **113**: 576, 1930.
40. Leadingham, R. S.: Tetralogy of Fallot: Report of a Case With Bacterial Endocarditis of the Pulmonary Valve and Collapse of Both Lungs, Ann. Int. Med. **4**: 620, 1930.
41. Segall, H. N.: A Case of Tetralogy of Fallot: Clinicopathological Observations. Quantitative Studies of Circulation Rate and the Right to Left Shunt, AM. HEART J. **8**: 628, 1933.
42. Campbell, J. M. H., Hunt, G. H., and Poulton, E. P.: An Examination of the Blood Gases and Respiration in Disease, With Reference to the Cause of Breathlessness and Cyanosis, J. Path. & Bact. **26**: 234, 1923.
43. D'Autrebande, L., Marshall, W. R., and Meakins, J. C.: Studies of Circulation in Three Cases of Morbus Caeruleus, J. Clin. Investigation **8**: 123, 1929.
44. Uhlenbruck, P.: Untersuchungen an einem autoptisch kontrollierten Fall von Pulmonalstenose, Ztschr. f. Kreislaufforsch. **19**: 601, 1927.
45. Schoen, R., and Derra, E.: Untersuchungen über die Bedeutung der Zyanose als klinisches Symptom, Deut. Arch. f. klin. Med. **168**: 52, 1930.
46. Mayer, C. P., and Israel, J. E.: La cianosis de una cardiopatía congénita. Estudio de los gases alveolares y de la sangre, Rev. Asoc. méd. argent. **48**: 113, 1934.
47. Pijoan, M., and Bérard: Une nouvelle méthode de diagnostic des communications cardiaques arterio-veneuses, dans les cardiopathies congénitales, Compt. rend. Soc. de biol. **122**: 411, 1936.

THE DISTRIBUTION OF SURFACE POTENTIAL ON THE CHEST IN INTRAVENTRICULAR BLOCK

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RECENTLY we re-examined a series of 176 cases of intraventricular block,[1] and found that they fall into four major categories: the common, the uncommon, and the first and second indeterminate types.

In the *common type*, QRS_1 is upright and of the $\wedge$ or $|/|$ type (with the first inverted phase tiny), and T_1 is inverted or diphasic, whereas QRS_3 is usually inverted and of the V or N type (but may be upright), and T_3 is usually upright (but may be inverted).

In the *first indeterminate type*, QRS_1 is upright and of the N or W type, and T_1 is inverted or diphasic; it differs from the common type in having a small inverted final phase; QRS_3 is usually inverted and of the N or M type, and T_3 is upright.

In the *second indeterminate type*, QRS_1 is diphasic and of the N type, with a deep, prolonged S_1; T_1 is usually upright. It differs from the uncommon type in having QRS_1 diphasic instead of mainly inverted.

In the *uncommon type*, QRS_1 is inverted or mainly inverted and of the N, or rarely V, type; usually there is a deep S_1, and T_1 is upright. QRS_3 is upright, and T_3 is usually inverted.

Measurements of the Q-E interval, namely, the interval from the onset of QRS to the onset of the subclavian arterial pulse, led to the conclusion that the common type of intraventricular block is most often associated with delay in the left ventricle, and that the uncommon and the two indeterminate types are not associated with delay in the left ventricle, hence, presumably, with delay in the right ventricle.[1] However, exceptions were found; especially frequent was the lack of evidence of Q-E prolongation in the common type of intraventricular block.

It seemed to us that this view could be checked further by ascertaining the distribution of the surface potential over the chest during various phases of the inscription of QRS, utilizing the method previously described by us.[2] For this purpose leads were taken entirely encircling the chest at the levels of the second and of the fourth intercostal spaces at the sternal margin in twelve of these cases of intraventricular block.

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RESULTS

Chest Lead Variations in the Different Types of Intraventricular Block.—Typical examples of the records obtained are shown in Figs. 1 to 6.* The chest leads in all of the types of intraventricular block which were studied showed a relationship to the limb leads similar to that reported for normal and hypertrophied hearts,[2] namely:

1. The left midaxillary chest lead at the level of the fourth intercostal space was usually almost the exact inverse of Lead I.

2. Leads at the right scapular region and the right posterior axillary area at the level of the second intercostal space were almost identical with Lead II.

3. Leads in equivalent positions on the left side were almost identical with Lead III.

4. The S-T and T segments tended to form a single, continuous element.

5. In the chest leads, as in the limb leads, in these cases of intraventricular block, the T wave showed a tendency to be directed opposite to the major or prolonged phase of QRS.

In addition, it was found that, when one viewed the entire series of chest leads in a case, there was a greater uniformity between cases than is apparent when any pair of chest leads is compared.

In the common type of intraventricular block the chest leads are characterized by large QRS deflections at many points; they are either of the V or $\wedge$ type, or of the N or |/| type, and in the latter have a tiny preliminary phase. W or M types of QRS either are not seen or appear in only one or two positions, but N or |/| types, with the two phases of approximately equal amplitude, occur at a number of points. The contour resembles that of left ventricular preponderance, except that QRS is prolonged. In all the cases QRS was downward, or mainly so, in the fourth intercostal space in the posterior part of the left axilla. Elsewhere, the direction of QRS was more variable. It may be entirely upright when the QRS in Leads II and III is also upright (concordant type), or, as in Fig. 1, when QRS is up in Lead II. It may be entirely upright over the central part of the front of the chest in the fourth intercostal space, as in Fig. 2, or entirely downward throughout the upper chest. With this wide variety of contours, it is difficult to see how the semidirect lead concept developed by Wilson, et al.,[4-6] can be held, for all of these varieties are considered by their school to indicate left bundle branch involvement. The variation is accounted for more readily by the field theory developed by us, as will be shown below.

The indeterminate and uncommon types of intraventricular block have smaller QRS amplitude, and, at many points, W- and M-shaped

*The chest leads shown are the inverted images of those recommended by the American Heart Association Committee on Precordial Leads.[3] This is due to the fact that they were taken before the above recommendation was published.

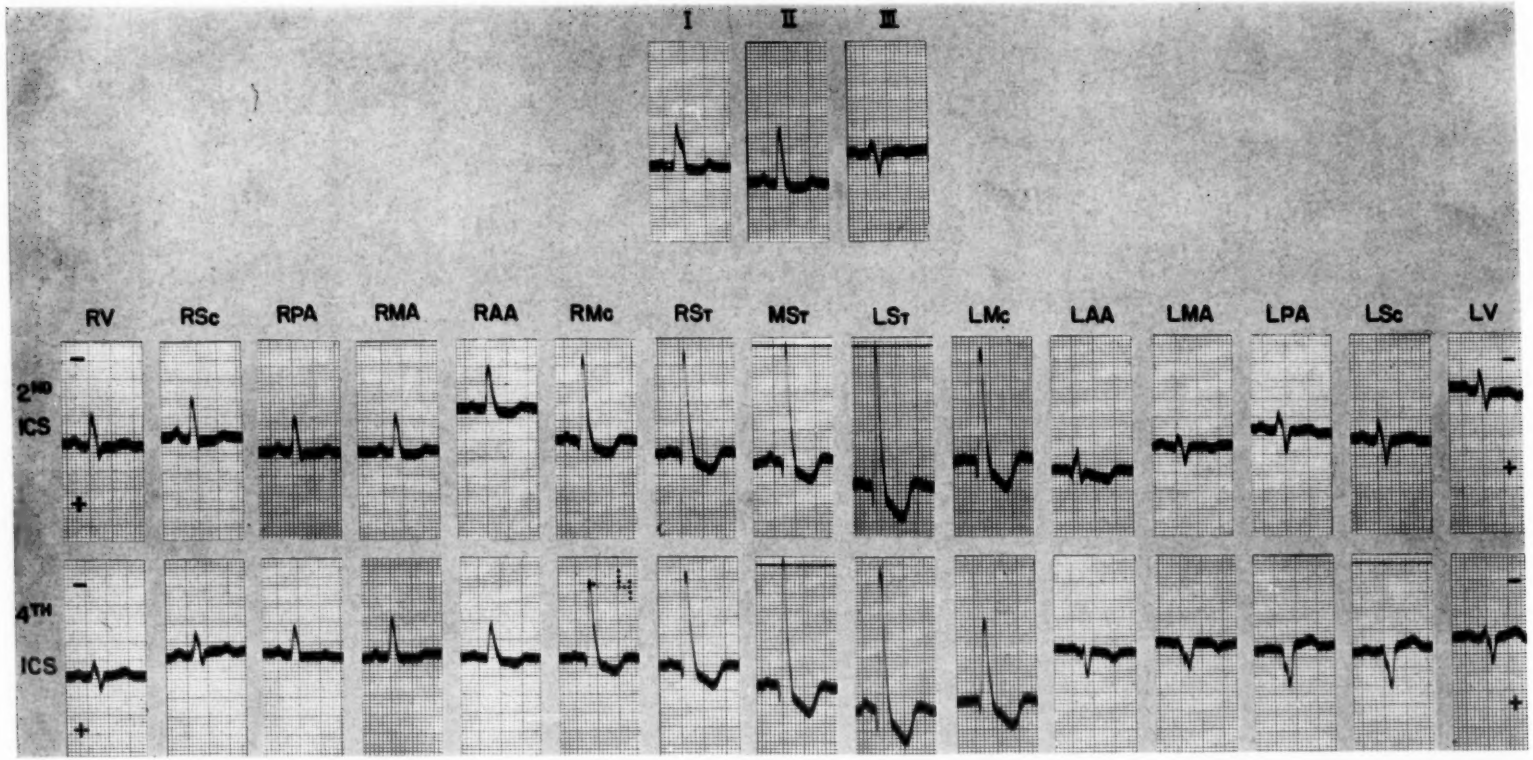

Fig. 1.—Electrocardiograms obtained on a patient with the common type of intraventricular block. In this and in Figs. 2 to 6 the standard limb leads, I, II, and III, are at the top of the figure; the middle row, labeled *2 ICS*, indicates chest leads taken at the horizontal level of the second intercostal space at its junction with the sternum; the left leg was the distant electrode, and the exploring chest electrode was placed at the right paravertebral line (*RV*), the right scapular line (*RSc*), the right posterior, middle, and anterior axillary line (*RPA, RMA, RAA*), the right midclavicular line (*RMc*), the right parasternal line (*RSt*), the midsternal line (*MSt*), and at homologous points on the left side of the chest (*LV, LSc, LPA, LMA, LAA, LMc, LSt*); the lower row, labeled *4 ICS*, indicates equivalent leads taken at the horizontal level of the fourth intercostal space at its junction with the sternum. The lead connections of the chest leads were the reverse of those recommended by the American Heart Association Committee. The curves are therefore inverted images of those obtained when the Committee's recommendation is followed, and are directly comparable with Leads II and III. The direction taken by the tracing when the polarity of the chest electrode becomes relatively negative and positive is shown by – and +. Discussed in text.

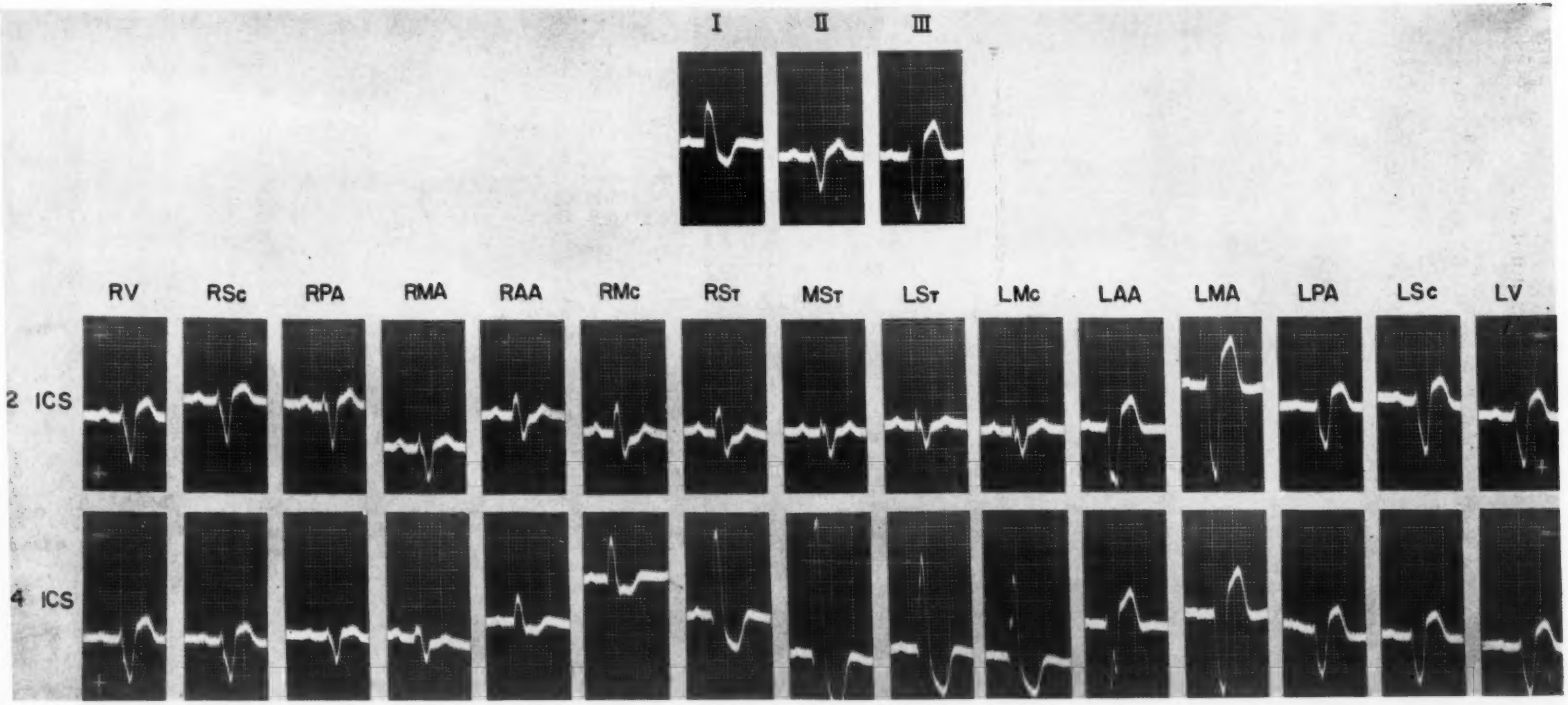

Fig. 2.—Electrocardiograms obtained on a patient with the common type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

QRS complexes are seen. The former occur especially over a small region on the front of the chest in the fourth intercostal space, and have phases of about equal magnitude; no large V or $\wedge$ types of QRS are found. In addition to the W type, N or |/| types of QRS, in which only the second phase is prolonged, are seen at other points. This is especially frequent in the second indeterminate type (Figs. 3 and 4), and in the uncommon type (Fig. 5). In the first indeterminate type, large inverted QRS complexes of the M type are recorded from the left axilla, as in Fig. 6. This does not occur in the second indeterminate or uncommon form. These contours, again like those in the common form, are readily accounted for by the field theory developed below.

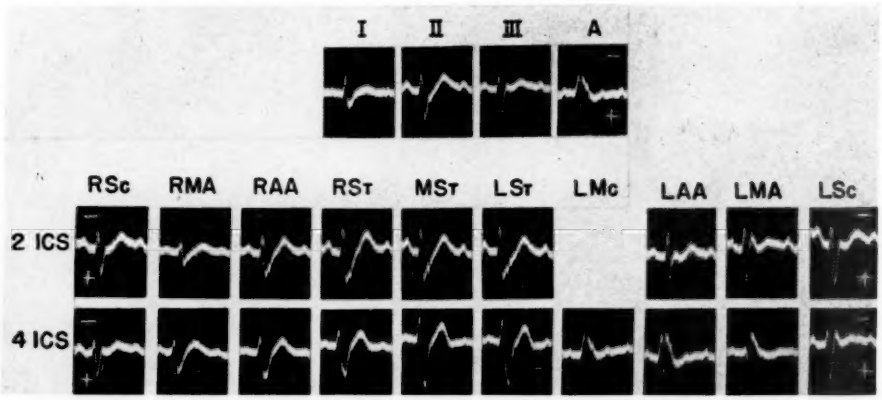

Fig. 3.—Electrocardiograms obtained on a patient with the second indeterminate type of intraventricular block. Conventions as in Fig. 1. *A*, in top row, is a lead with the chest electrode over the apex. Discussed in text. At autopsy this heart showed multiple infarcts.

It is thus apparent that intraventricular block can be distinguished in the chest leads in the same way as in the limb leads, and that, by studying both limb and chest leads, the type can be more clearly established than from limb leads alone.

The Distribution of Surface Potential as Ascertained From Chest Leads in the Various Patterns of Intraventricular Block.—In our previous communication[2] we pointed out that the chest leads gave information concerning the surface distribution of the electrical field created by the heart, and that this could be correlated with the character of the spread of the impulse and the spread of the restitution process through the heart chambers. The modifications caused by hypertrophy of the heart were shown to be in harmony with alterations in the mass and position of the heart, and did not require the assumption that any particular region of the heart determined the character of the deflections in any particular chest lead. This general conclusion is supported by the evidence obtained from the cases of intraventricular block reported here.

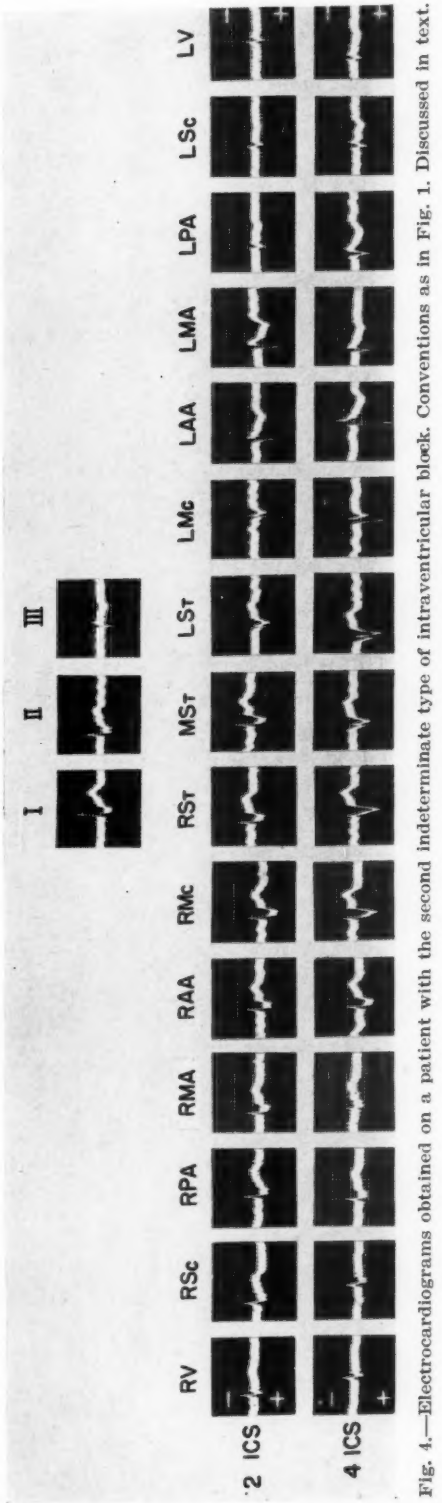

Fig. 4.—Electrocardiograms obtained on a patient with the second indeterminate type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

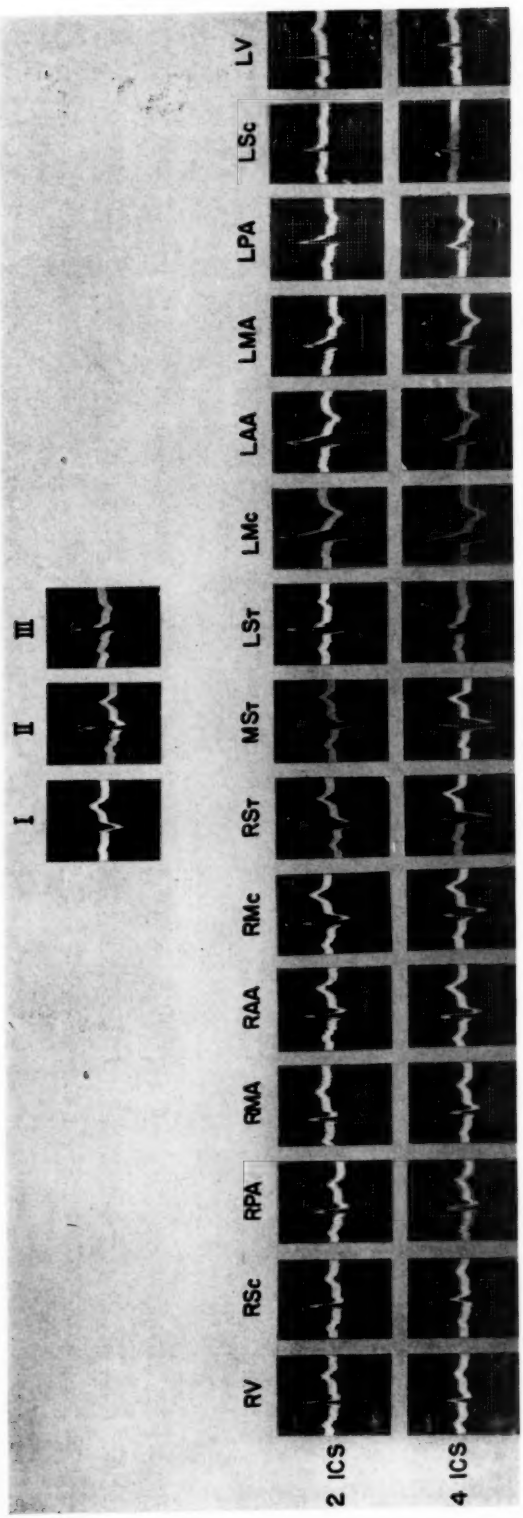

Fig. 5.—Electrocardiograms obtained on a patient with the uncommon type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

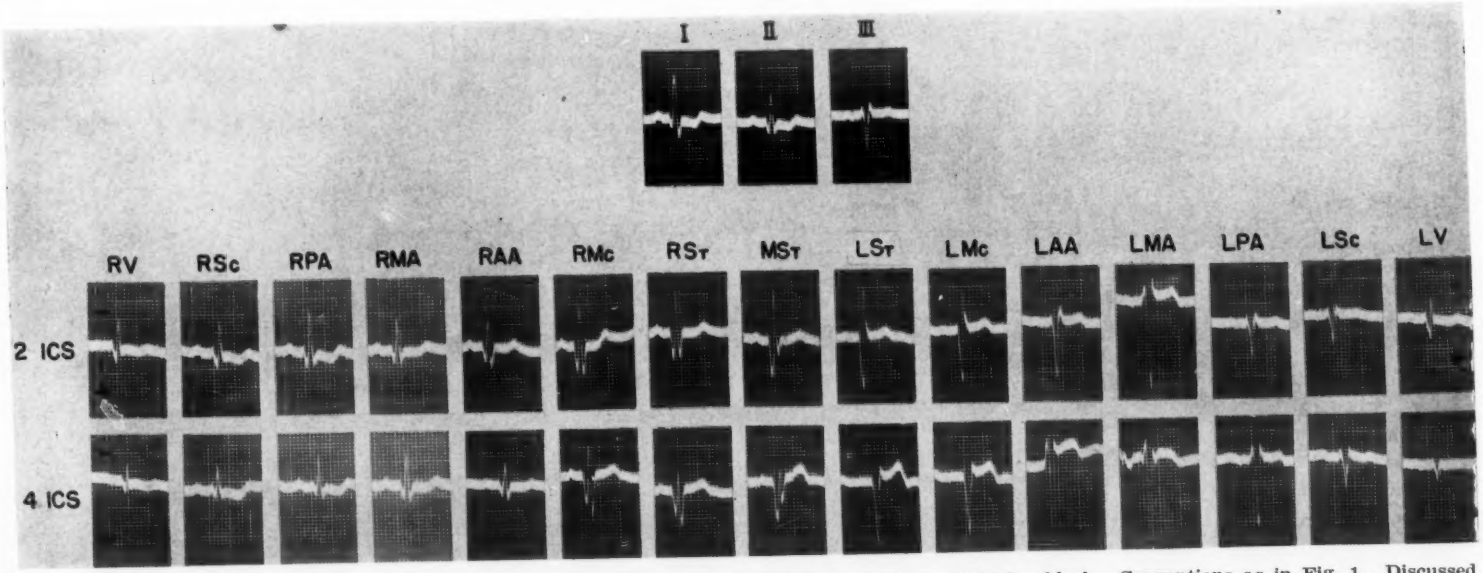

Fig. 6.—Electrocardiograms obtained on a patient with the first indeterminate type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

The surface potential distribution at given instants of the heart cycle, namely, during the inscription of QRS and T, was measured in the manner described before, and the charts of the zero potential and of maximum negative and positive potential in the horizontal plane at the level of the fourth intercostal space were constructed in the same manner.

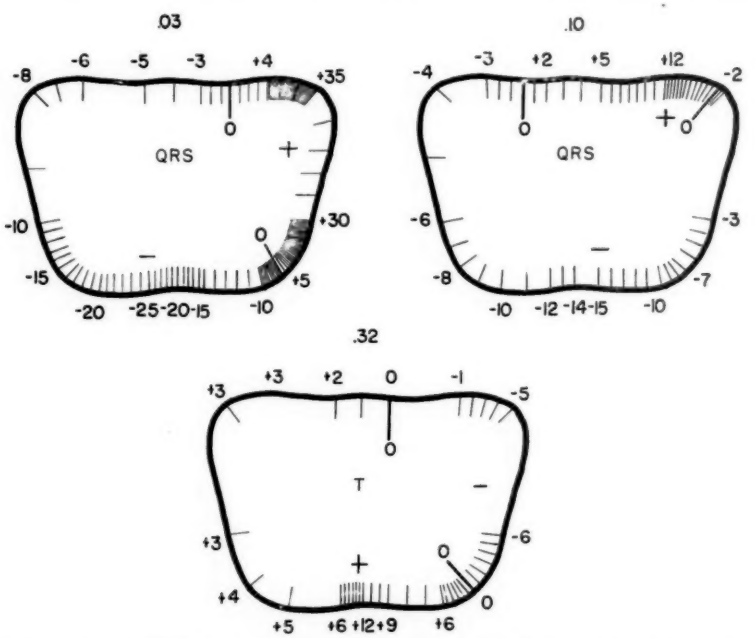

Fig. 7.—Cross-section diagrams representing the distribution of surface potential at the horizontal level of the sternal end of the fourth intercostal space in a case of the common type of intraventricular block (concordant variety). The several diagrams illustrate the state of affairs 0.03, 0.10, and 0.32 sec. after the onset of QRS; the first two are during the inscription of QRS, the last, during the inscription of T. Potential values are expressed in terms relative to leg potential, in multiples of 0.1 millivolt. The zero potentials are emphasized, and the maximum positive and negative potentials indicated. Discussed in text.

The same qualifications concerning quantitative accuracy, as previously stated, held here also. This is due to the fact (1) that absolute synchrony of the points of time selected in the various leads cannot be guaranteed, (2) that the leg (''indifferent'') electrode is not at ''zero'' potential throughout the heart cycle, and (3) that neutralization of constant body current and injury currents from the heart before taking the record does not permit evaluation of the true potential levels at each point. Nevertheless, these inaccuracies do not nullify the value of the approach as a first, rough approximation, and do not militate against the deductions reached. The surface fields are shown in Figs. 7 to 13 for the patients whose electrocardiograms are illustrated in Figs. 1, 2, 4, 5, and 6, and for two whose electrocardiograms are not shown; of the latter, one was of the concordant upright type, and the other, of the common type, with QRS downward over the entire chest.

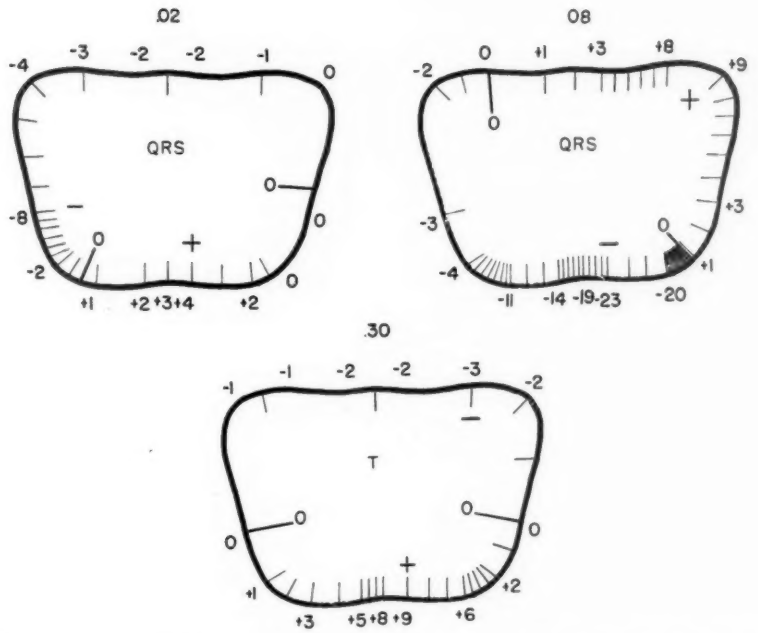

Fig. 8.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 1) of the common type of intraventricular block. The several diagrams illustrate the state of affairs 0.02 and 0.08 sec. (during QRS), and 0.30 sec. (during T) after the onset of QRS. Discussed in text.

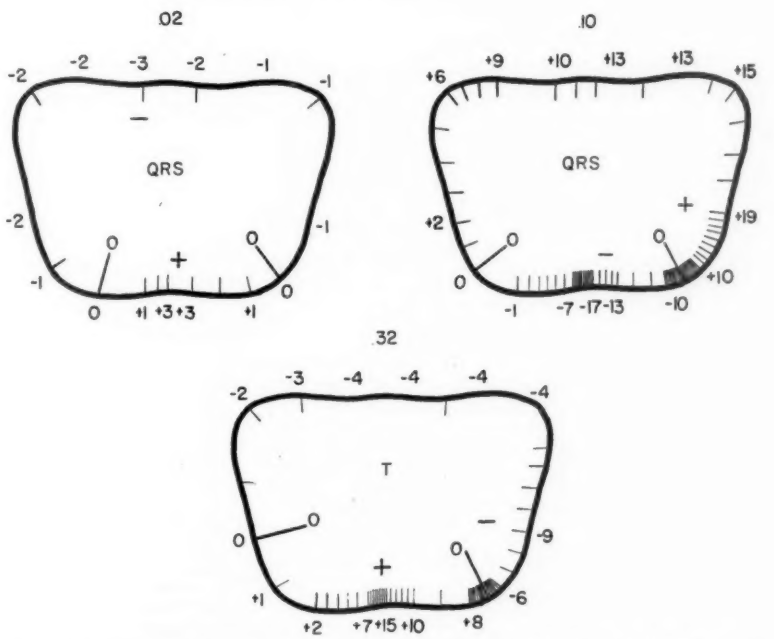

Fig. 9.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 2) of the common type of intraventricular block. The several diagrams illustrate the state of affairs 0.02, 0.10 (during QRS) and 0.32 sec. (during T) after the onset of QRS. Discussed in text.

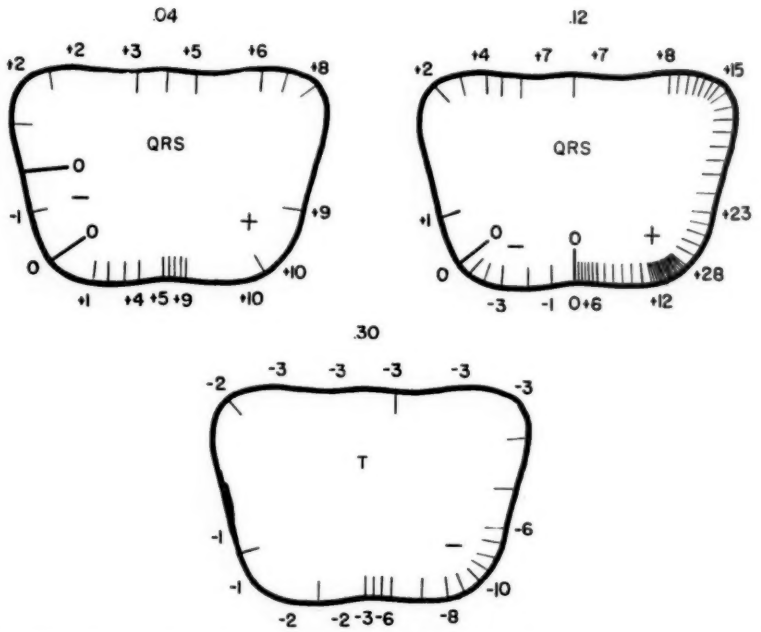

Fig. 10.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in another case of the common type of intraventricular block with QRS downward in the chest leads. The several diagrams illustrate the state of affairs 0.04, 0.12 (during QRS), and 0.30 sec. (during T) after the onset of QRS. Discussed in text.

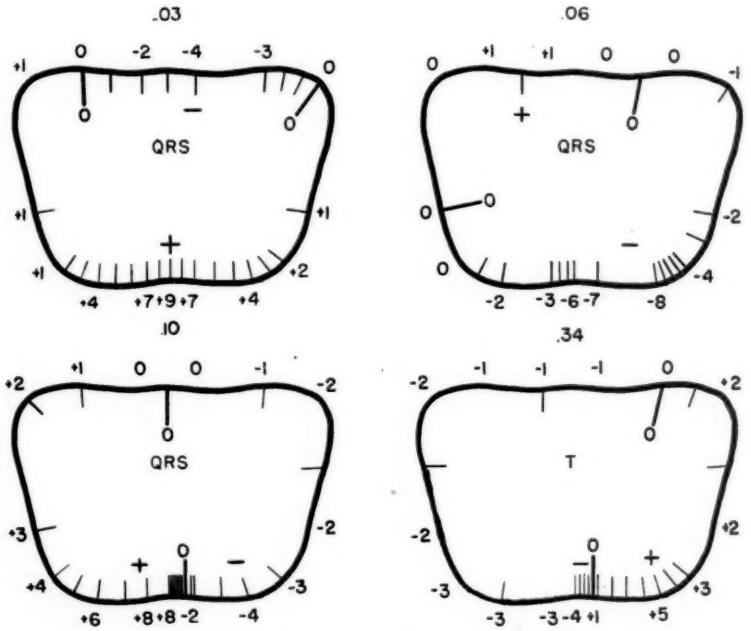

Fig. 11.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 5) of the uncommon type of intraventricular block. The several diagrams illustrate the state of affairs 0.03, 0.06, 0.10 (during QRS), and 0.34 sec. (during T) after the onset of QRS. Discussed in text.

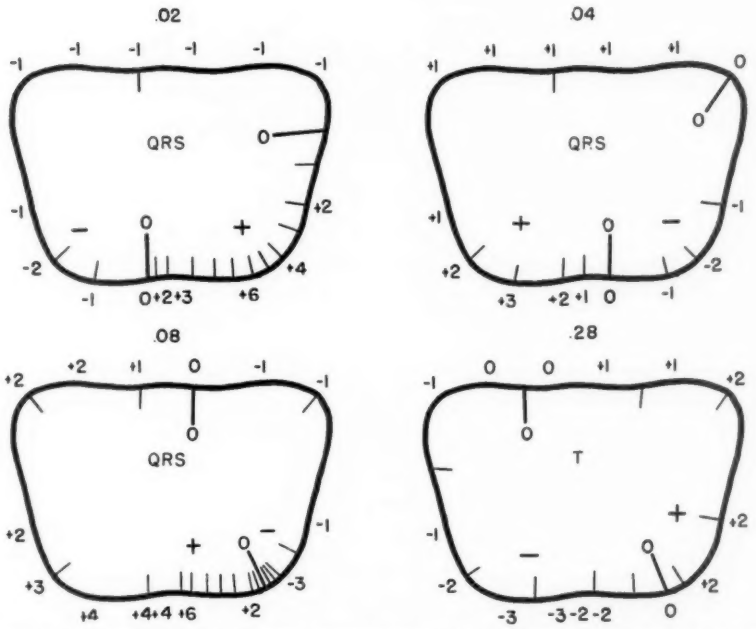

Fig. 12.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 4) of the second indeterminate type of intraventricular block. The several diagrams illustrate the state of affairs 0.02, 0.04, 0.08 (during QRS), and 0.28 sec. (during T) after the onset of QRS. Discussed in text.

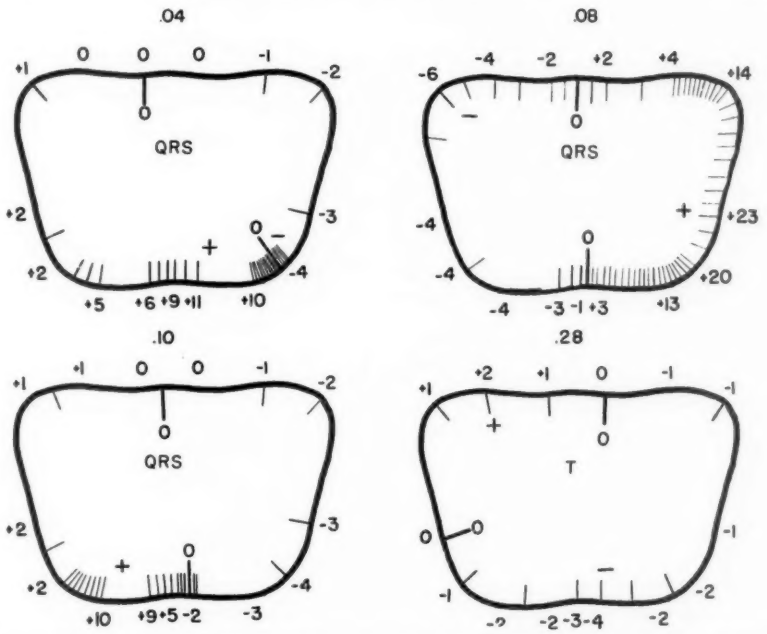

Fig. 13.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 6) of the first indeterminate type of intraventricular block. The several diagrams illustrate the state of affairs 0.04, 0.08, 0.10 (during QRS), and 0.28 sec. (during T) after the onset of QRS. Discussed in text.

In intraventricular block, as work from this department has shown, the effect of the block itself must be differentiated from the associated changes in heart contour, mass, and position.[7-10] Both will influence the three dimensional character of the spread of the impulse and of the restitution processes which are responsible for the creation of the electrical field during QRS and T.

Variations in the field will thus be determined (1) by the location of the block or blocks, since more than one site may be involved, and these need not be precisely the same from heart to heart, and (2) by differences in the contour and position of the heart and the mass of its various chambers.

The chief difference between the common type of intraventricular block and the other varieties is the fact that the former has two phases in the development of the field during the spread of the impulse (QRS), and the latter have three. There are, in addition, striking differences in the direction of the field both during the spread of the impulse and during restitution. The differences will be more apparent after discussing the surface field in each type and subdivision of intraventricular block.

In the common type of intraventricular block there was a similarity of the surface fields in the four cases shown which is typical of the series; the differences are chiefly that zero lines vary in their initial position and rotate to different degrees in a clockwise direction when viewed from above, and that in one form (Fig. 10) the negative field seems to be located chiefly posteriorly, below the level of the fourth intercostal space. Further, the electrical field during inscription of the T wave is opposite in direction to that during the inscription of most of QRS. The field developed during the inscription of QRS in common intraventricular block resembles that in left ventricular preponderance, and so does that of the T wave, aside from the time constants. This would indicate that the spread through the left ventricle dominates the electrical field, and so lends support to the view that the block is chiefly, if not entirely, in the left ventricle. The restitution is such as to indicate a lag of recovery in the left ventricle, which would also support the view that the block was chiefly in the left ventricle.

The variations among these patients in the pattern of the fields is attributed, as mentioned above, to differences in the position of the heart, the relative hypertrophy of the two ventricles, and the exact location of the areas of block. Some clue as to the degree to which hypertrophy of the left ventricle determines the field can be obtained from a knowledge of the degree of hypertrophy present and from the amount of prolongation of the Q-E interval. The shorter the Q-E interval and the greater the left ventricular hypertrophy, the more must the deviation from normal in the field be ascribed to the hypertrophy.

Other influences, notably, loss of large masses of muscle as a result of disseminated, small and confluent, recent or healed infarcts will likewise play their role in altering the electrical field.

In the uncommon type of intraventricular block, the first two phases of QRS have fields similar to normal, but the third phase is so oriented as to indicate a delayed spread of the impulse through the right ventricle. This last is also true of the field during the inscription of the T wave. In short, only after the impulse has spread through most of the left ventricle does the dominance of the right ventricle become clear. Of course, the time at which this occurs would vary with other circumstances, as discussed above, but mostly with degree of hypertrophy of the right and left ventricles.

The close resemblance of the field in the second indeterminate type of intraventricular block to that in the uncommon type confirms the former's close relationship to the uncommon type of block, and supports the view that the two are of similar origin.

In the case of the first type of indeterminate block the conditions are more complex. In the first and third phases, the electrical field shows dominance of the right ventricle, but in the second phase this is not present, and, during the inscription of T, there is evidence of dominance of the left ventricle. This could be produced by any of three combinations, viz., (1) left ventricular preponderance, with block primarily in the path to or in the right ventricle, (2) right ventricular preponderance, with block primarily in the left ventricle, or (3) block involving both ventricles to an approximately equal degree. In these ways one could account for the varying dominance of the two ventricles on the electrical field. Examination of the heart for such hypertrophy, and the Q-E interval, would help to evaluate the presence of block in the left ventricle.

The evaluation obtained from such electrical field studies therefore lends support to the deduction arrived at from Q-E duration measurements in determining the location of intraventricular block.[1] In general, the deductions are in accord with those now established as a result of the work of Wilson and his school,[4-6] but with some modification. Our results, however, although they lend support to the views concerning location of the block arrived at by Wilson, do not support his interpretation as to the meaning of the chest leads. The present study gives further evidence that the chest leads are not "semidirect" leads, as Wilson has argued, but rather depict, at a given point on the chest, the orderly alteration of the electrical field created by the passage of the impulse throughout the heart (and the restitution process), without the exertion of undue influence by the activity of the region of the heart beneath the electrode upon the potentials the latter records.

SUMMARY AND CONCLUSIONS

1. Intraventricular block is diagnosed in the electrocardiogram when the duration of QRS is 0.12 sec., or more, in the limb leads. It can be classified into four types, according to the electrocardiographic appearance, viz., the common, the uncommon, and the first and second indeterminate types. The chest leads in these groups fall into definite patterns.

2. The chest leads represent primarily the fluctuations in the electrical field of the region beneath the chest electrode during the spread of the impulse and during the restitution process throughout the heart. There is no reason to assume that there is dominance of any part of the heart over any other; all parts seem to play an approximately equal role in producing these electrical effects. The manner in which the impulse spreads and the restitution process occurs in the various regions of the heart appears to be the determining factor in establishing the electrical field.

3. These studies confirm and expand the views developed by us previously regarding the genesis of the electrocardiogram.

4. These studies confirm our observations in regard to the Q-E interval. They show that, although other influences, such as hypertrophy and displacement of the heart, as well as the causes which lead to low voltage, affect the appearance of the electrocardiogram in intraventricular block, the various types, by and large, appear to represent definite types of delay in the spread of the impulse, namely:

(a) The common type of intraventricular block appears to represent chiefly delay in the left ventricle.

(b) The uncommon and second indeterminate types of intraventricular block appear to represent chiefly delay in the right ventricle.

(c) The first indeterminate type of intraventricular block appears to represent a mixture of delay in the right and left ventricles.

We are indebted to several interns of the department for their assistance in obtaining the electrocardiograms.

REFERENCES

1. Bohning, A., Katz, L. N., and Langendorf, R.: Intraventricular Block. AM. J. M. SC. (in press).
2. Bohning, A., Katz, L. N., Robinow, M., and Gertz, G.: Value and Significance of Multiple Chest Leads in Man; Normal and Hypertrophied Hearts, AM. HEART J. **18**: 25, 1939.
3. Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland: Standardization of Precordial Leads, AM. HEART J. **15**: 107, 235, 1938. Also J. A. M. A. **110**: 395, 681, 1938.
4. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, AM. HEART J. **7**: 305, 1932.
5. Wilson, F. N., Johnson, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, AM. HEART J. **9**: 459, 1934.

6. Wilson, F. N., Johnson, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle Branch Block, AM. HEART J. 9: 472, 1934.
7. Katz, L. N.: Recent Advances in the Interpretation of the Electrocardiogram, J. A. M. A. 97: 1364, 1931.
8. Katz, L. N., and Ackerman, W.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles, J. Clin. Investigation 11: 1221, 1932.
9. Ackerman, W., and Katz, L. N.: Reversal in Direction of the Q-R-S Complex of Experimental Right Bundle Branch Block With Change in the Heart's Position, AM. HEART J. 8: 490, 1933.
10. Kissin, M., Ackerman, W., and Katz, L. N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle Branch Block in Man, Am. J. M. Sc. 186: 721, 1933.

THE CHANGES IN THE FORM OF THE BEATING MAMMALIAN HEART, AS DEMONSTRATED BY HIGH-SPEED PHOTOGRAPHY

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IN 1939, Landis, Hunt, Moe, and Visscher[1] prepared a series of cinematographic films of the beating mammalian heart. The preparations photographed were the heart in situ, the heart-lung preparation, and the isolated heart. Although the films were prepared for general observation and study, it is believed that sufficient information was acquired to justify recording it permanently. Other investigators have used cinematographic records in the study of the heart movements, but in the present work ultra high-speed photography was the novel feature.

METHODS

The photography was done with three cameras; one had the usual speed of 24 frames in one second; another had a maximum speed of 600 frames in one second; and the third had a maximum speed of about 3,000 frames a second. If the films obtained from the latter cameras were projected at a speed of 15 frames per second, one observed a marked slowing effect on the cardiac movements. This effect, which may be called temporal magnification, would have maximum values of 40 and of 600 times. In the portion of the films which we have used for analysis, the moderately high-speed camera (called "super") took frames at an average rate of 100 per second, and the very high-speed camera (called "hyper") took frames at an average rate of 1,200 per second. A clock was photographed simultaneously, so that the interval between any two of the exposures could be ascertained accurately.

The interpretation of the films has been pursued in various ways. The longest time was spent in repeatedly reviewing the films on numerous occasions and noting phenomena as they appeared. The evidence based on these observations is the testimony of several witnesses who were in agreement. In regard to the heart shape and its changes, we have traced numerous consecutive frames on the reverse side of a transparent screen, and have had prints made of certain frames. These latter methods have supported our opinions in regard to heart shape which were obtained by direct observation.

Another method of study which contributed to the analysis of the cardiac motion was the tracing of the movement of reference points on the reverse side of a transparent screen while the projector was running. A second observer checked the exact time, by the clock shown on the film, as each point was marked. In this way the exact temporal relationships of movement of various points on the ventricular surfaces were obtained.

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THE SHAPE OF THE HEART IN SYSTOLE AND DIASTOLE

It will be readily recalled that, when the thoracic cage is opened, and particularly when the heart is removed therefrom, this organ loses the support of its semifluid environment and the influence of the negative intrathoracic pressure. The heart is then more subject to change in shape, and this shape distortion will be that of flattening. The latter will be functions of the intraventricular tension and myocardial elasticity. The isolated normal dog's heart, when in good condition, shows considerable flattening, particularly when its base and apex lie in a horizontal plane. In hearts suffering under a greatly increased load, very little flattening is seen. This has been interpreted as indicating that the diastolic volume has increased to a point where the ventricular wall cannot lengthen without considerable increases in intraventricular pressure.

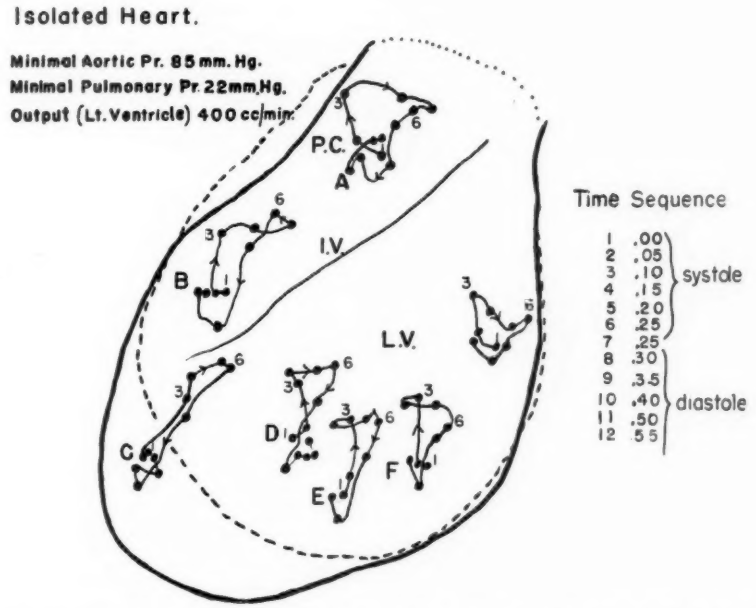

Fig. 1.—A ventral, inferior view of an isolated heart, showing the course of reference points on the epicardium during the cardiac cycle. Dots of the same number indicate synchronous positions in the spatial course of any reference point. To be particularly noted are the early lateral direction of point *A* (from *1-3*), indicating early distension of the pulmonary conus, and the early marked movement of points *B* and *C* in the long axis of the heart, indicating a shortening of this axis. The various reference points are labeled *A, B, C, D, E, F*. *PC*, Pulmonary conus; *IV*, interventricular groove; *LV*, left ventricle. To avoid complication of the figure, only the synchronous positions *1, 3*, and *6* are numbered. From these numbers the sequence of the dots from *1* to *13*, with intervals representing 0.05 sec., can be readily followed. The line between any two dots, representing space over unit of time, is actually a measure of velocity, as well as of direction of movement.

The isolated heart, when lying on its side, will thus have the shape of a bulging cone flattened in its vertical diameter. With the onset of systole, the heart approximates a spherical shape very rapidly, and the gross

movements of the ventricular wall in systole are attributable to the shape differences in diastole and systole. Throughout the ejection period the heart maintains its close approximation to the spherical shape. The degree of rotation of the heart and torsion of its apex during systole varied in different hearts, and was seemingly dependent upon the diastolic and systolic volumes.

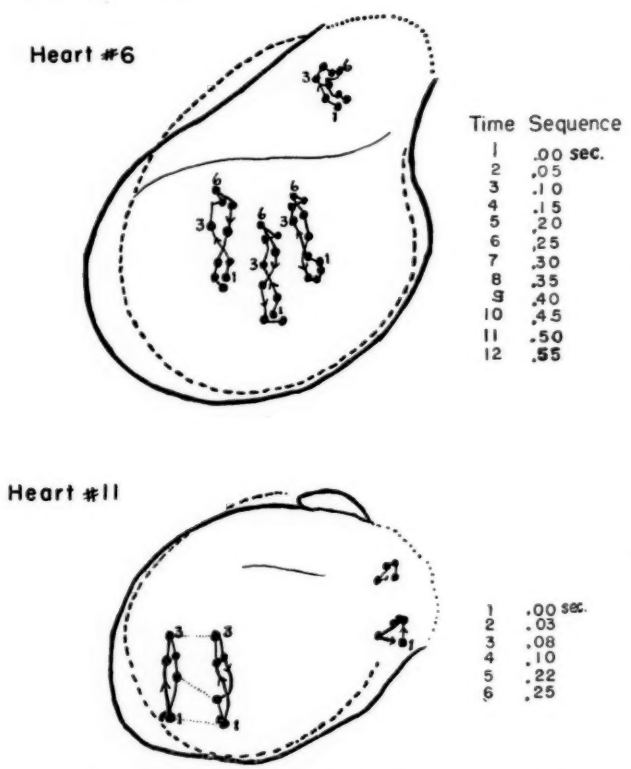

Fig. 2.—Direct apical views of two hearts, showing the course of reference points during the cardiac cycle. In Heart No. 6 the movements are mainly in an antigravity direction; this we attribute to change in shape and a lifting of the apex. A slight clockwise rotation is demonstrable by joining positions with the same number. The movement of the point on the pulmonary conus is similar in type to that in Fig. 1, but the curve is distorted due to its position in the background of the photographic field.

In Heart No. 11, there is much more torsion during systole; the heart turned about 40° clockwise, after a slight counterclockwise movement. During the rotation, the point on the auriculoventricular groove did not move appreciably, indicating that the movement was entirely a torsion ("wringing") movement, without any definite rotation of the whole organ.

By following reference points on the ventricular surfaces and their time relationships, a clear picture of the heart movements may be obtained (Figs. 1 and 2). It is observed that all points on the ventricular surfaces rise rapidly during the first third of systole (between *1* and *3* in Fig. 1), and this is to be attributed to the fact that the heart assumes a spherical shape. This is further to be noticed by following the course of points *B* and *C*, in Fig. 1, where there is a clear demonstration

of a shortening of the long axis of the heart in early systole. Again, with reference to the course of the points on the left ventricle, it may be observed that the apex early in systole shows a torsion effect, with a slight rotation contraclockwise, followed, however, by a more marked rotation in the clockwise direction immediately before the onset of diastole. These movements can be demonstrated in Fig. 1 by joining points of the same number, which are isochronic. This type of consecutive rotation, which we have observed repeatedly, could be related to the superficial and deep musculospiral bundles of the heart, which lie roughly at right angles to one another.

In the tracing of point *A* (Fig. 1), the first part of the curve represents the distension of the pulmonary conus in early systole, which is readily seen on direct observation. The next part of the curve shows a rapid upward rise, due mostly to a rising of the whole heart, then a slight rotatory effect counterclockwise, followed by a clockwise rotation of the whole heart, as demonstrated by a movement of the reference point towards the right. In the tracings of points on the apex, the curves may be mainly in a vertical direction (Fig. 2). The slight, though definite, evidence of rotation in Heart No. 6 can probably be explained in part by the fact that these points are very close to the axis of rotation.

It will be readily appreciated that these figures represent movements of points in three dimensions, as projected on a frontal plane. This fact, together with slight indistinctness of the borders of the reference points and machine vibration, makes it impossible to obtain any very accurate measurements between any two points during the latter part of systole.

When the heart is distended, i.e., approaching its maximum diastolic volume, it maintains a roughly spherical shape throughout the whole cycle, and the movement of systole is to be made out with some difficulty. This slight movement is readily understood when one remembers that the ejected blood is changing the volume of a sphere which is a function of the cube of the radius. In such distended hearts we have been unable to observe apical rotation, and it is our belief that the "wringing-out" contraction occurs only at small systolic volumes.

SPECIAL CONSIDERATIONS REGARDING THE RIGHT VENTRICLE

This study has been illuminating with respect to the events which occur in the right side of the heart, particularly in regard to a differentiation of the right ventricle into inflow and outflow tracts, as emphasized anatomically by Kirch.[2] During systole, we have said that the ventricle approximates the shape of a sphere. Actually, the cavity of each ventricle would tend to assume a spherical shape, and, because of the higher pressure in the left ventricle, the systolic shape of the heart would be determined by the left ventricle, with the right ventricle acting as an

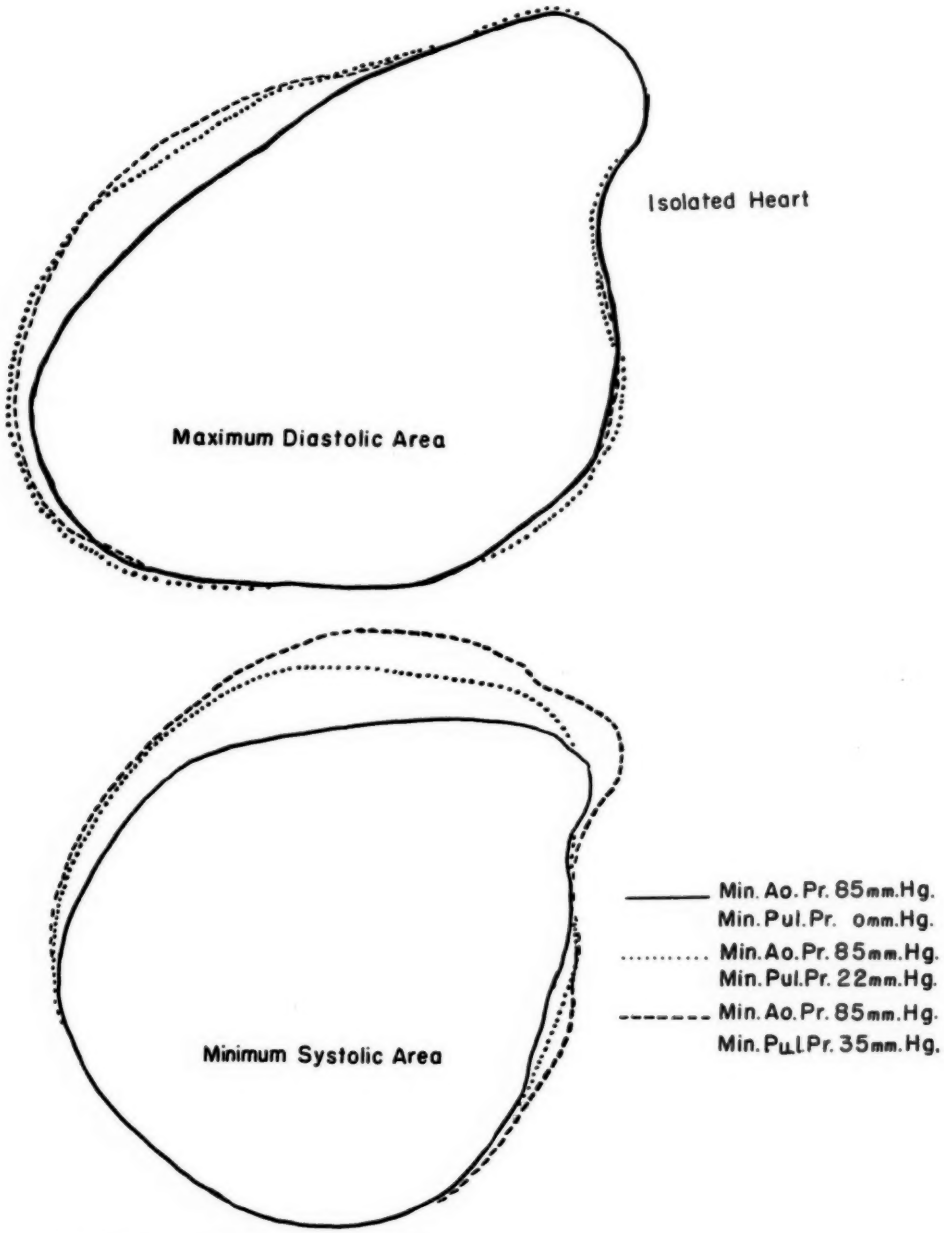

Fig. 3.—Figures obtained by tracings of the maximum diastolic and minimal systolic areas of an isolated heart. The areas are traced for three pulmonary pressures. It is to be noted that the diastolic shape remains about the same for the two higher pulmonary pressures. The flattened inferior aspect has been explained in the text. The heart rested on the table and was not otherwise supported. In all three systolic areas the close approximation to a circle is a noteworthy feature. With increases in pulmonary pressures there is an increasing distension of the pulmonary conus, or, more accurately, the outflow tract of the right ventricle.

appendage. This theoretical consideration is in agreement with our observations. It seems an unequivocal fact that the cavity of the lower and posterior portion of the right ventricle is reduced in volume because of the spherical shape assumed by the left ventricle in early systole, so that the right ventricular blood is stored during the isometric contraction and early systolic period in the pulmonary conus (Figs. 3 and 4).

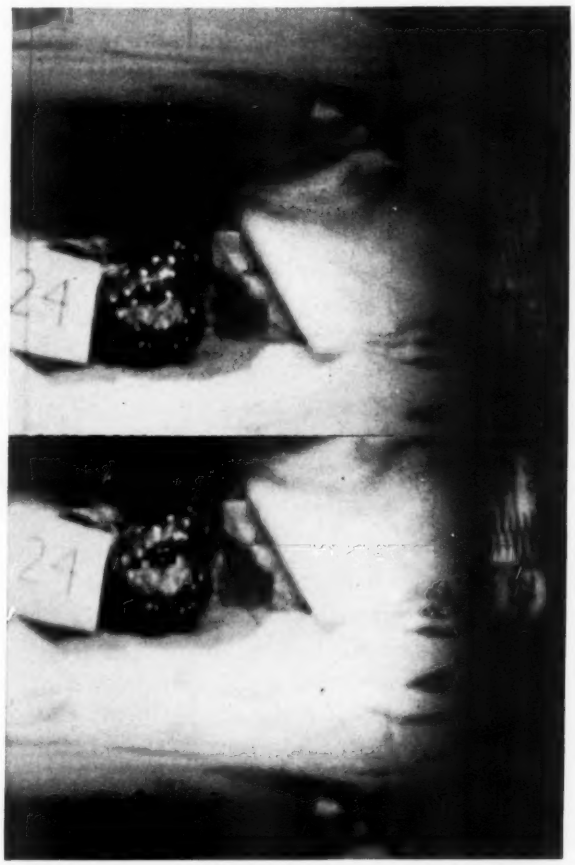

Fig. 4.—Reproductions of two photographic frames, showing the isolated heart at the end of diastole and 0.15 sec. later in mid-systole. The flattened shape of the heart and collapsed pulmonary conus are seen in the first photograph and the roughly spherical shape of the heart and distended pulmonary conus are seen in the second photograph. The movements of points on the surface of the heart were studied by following the displacement of the markers, which were small squares of white paper. The clock, marking hundredths of a second, is seen at the right of each frame.

With an increase in pulmonary blood pressure there is dilatation of the right ventricle in the region from the right ventricular apex to the pulmonary artery (outflow tract), which appears as a distended, tubular organ.[5] These observations are in agreement with the idea expressed by Kirch, namely, that dilatation begins in the outflow tract of the right ventricle when this chamber is under continued strain.

SYSTOLIC AND DIASTOLIC WAVES IN THE PULMONARY CONUS

Observations on systolic and diastolic waves in the pulmonary conus have given further support to the idea that the inflow and outflow tracts of the right ventricle exist as separate functional units. There is a considerable difference in the degree of distension of the pulmonary conus in systole which is dependent upon the diastolic volume and pulmonary pressure.

In a rapidly beating heart, photographed in situ, we have seen that the pulmonary conus was little filled in diastole. Then, with the onset of systole, the pulmonary conus and pulmonary artery have acted as a continuous unit; what might be called a "bolus" of blood passed quickly from the right ventricular apex into the pulmonary artery. With this mechanism of emptying, there is an early, rapid, slight caudad movement of the heart, or "recoil." Colloquially we have referred to this phenomenon as a "pistol-shot" ejection.

Under conditions in which the pulmonary conus contains a considerable amount of blood we have noted an early, faint systolic wave which was propagated rapidly over the pulmonary conus to the pulmonary valves, and then reflected backward toward the apex. We are tempted to believe that this rarely observed wave indicates that inflow tract blood is entering the outflow tract, and that it is probably related to contraction of the *left* ventricle because the latter chamber early assumes a spherical shape.

During diastole, the pulmonary conus is the site of an interesting wave. With low pulmonary pressures the conus of the right ventricle may be totally collapsed at the onset of diastole, and a fluid wave is frequently seen to pass from the apex to semilunar valves and back again in the same manner as a fluid wave might travel in a collapsed bicycle tube. As this wave takes from 0.12 to 0.15 second for its complete journey, it travels fairly slowly, probably about 1 meter per second. This wave is believed to accompany some of the first blood which enters the right ventricle from the auricle, causing a wave to travel back and forth in the outflow tract before pressures are stabilized. This surging diastolic wave in the pulmonary conus is best seen with a temporal magnification of about eight times. Inasmuch as the wave appears mainly as a sequence of high lights and silhouette changes, it cannot be illustrated here. The possibility that such waves might be related to the physiologic third heart sound has been entertained. That this wave might be the cause of the diastolic vibration that Kountz and his co-workers[3] have recorded seems a probability. The wave they described was usually of low frequency, without acoustic value, and occurred at the point occupied by the normal third heart sound, although the third heart sound might not be heard.

GENERAL COMMENT

There were several other phenomena that seem sufficiently interesting to record, although they only confirm what has been previously demonstrated in cardiac contraction. Following the administration of acetylcholine, the isolated heart showed periods of asystole lasting three to four seconds, and the first beat was manifested by a striking functional insufficiency of the tricuspid valve. The auricle became markedly distended with the ventricular contraction, and this could be correlated in time with the ventricular diminution in volume in its ejection period. This would indicate that, when there is prolonged asystole, the right auricle and ventricle form a common chamber and that the valve becomes insufficient as a result of the increased ventricular diastolic volume. We suspect that the marked venous pulse in the neck which is observed clinically with the returning cycle after an extrasystole, when the heart is beating slowly, is an analogous event.

After the administration of adrenalin, the increase in the force and rate of the cardiac contraction is readily followed. The upward stroke of the curves of the reference points is shortened in time, and the heart attains its spherical size so quickly that there is an "overshooting" due to the increased momentum, which produces a bouncing effect in the ordinary motion picture.

It has been shown by Visscher[4] that the partition of the coronary blood between coronary sinus and Thebesian drainage is a function of the aortic pulmonary pressure difference. It was suggested that increased pulmonary pressure played a nefarious role in right ventricular failure by interfering with the right ventricular blood supply, which is largely drained by the Thebesian system. The cinematographic records of the isolated heart show that distension of the right ventricle, produced by increments of pulmonary pressure, is improved by a later increase in aortic pressure. A quantitative study of this phenomenon has not been possible by this method of observation.

In a study of ventricular fibrillation high-speed photography did not contribute anything of exceptional interest. We have observed, however, that the onset of fibrillation may be characterized by undulatory movements of rather large masses of ventricular muscle. The later, finer, fibrillary movements and atonic phase, as described by Wiggers,[5] are not readily discernible in our records.

Our evidence regarding the geometrical changes caused by cardiac contraction is in accord with that of Brednow.[6] He also traced the course of reference points on the ventricular surfaces and noted particularly, as we have done, the shortening of the long axis of the heart. Our films were not taken with the view of correlating the cardiac output with the change between systolic and diastolic volumes. There are many

difficulties attendant on such calculations. Strughold[7] has maintained that cinematography in one plane is an accurate method of estimating the stroke output of the heart. His pictures were taken from a superior aspect, so that, as the heart rose to a spherical shape, the peripheral outline would become smaller, independent of the output. Whether his correction, which was based on checking the camera-object distance, was adequate is somewhat questionable. With a suspended, isolated heart, we believe that cinematography, from a lateral direction, would give accurate figures for systolic and diastolic size but as a method for the measurement of cardiac output it would be by no means void of assumptions.

It was hoped that ultra high-speed photography might give us data on the finer details of ventricular events and rapid vibrations of the heart wall, but in this we were disappointed. We have noted A-V conduction time from the mechanical events, but one could not claim adequate accuracy for the figures obtained.

We are fully aware that the dog's heart differs from the human heart in that the pulmonary conus is relatively longer, and the apex is formed entirely by the left ventricle, but we do not believe that such differences would invalidate the application of our results, in a limited way, to the human heart. It is stated generally that there is a counterclockwise rotation of the heart, as viewed from the apex. Species differences are possible, but, for the dog's heart, we are certain that the greatest rotatory effect is clockwise. If our observations on the storage of right ventricular blood in the pulmonary conus during systole can be transferred to the human heart, it may explain the occasional roentgenkymographic observation of paradoxical systolic movement of the upper left border of the human heart.

SUMMARY

The mechanics of cardiac contraction, as studied by high-speed photography, have been described. The study has brought forth strong evidence that, although the gross movements of the ventricular wall are related to changes in form, the diminution in volume in systole is roughly a function of changes in spherical size. For the dog's heart, it has been shown that the greatest rotatory torsion movement is clockwise; that is, the right ventricle occupies a greater percentage of the anterior (ventral) aspect of the heart. In these experiments we obtained confirmatory evidence that the right ventricle is composed of two distinct units, namely, the inflow and the outflow tracts. An early diastolic wave over the pulmonary conus which is reflected back from the closed semilunar valves is seen with regularity.

REFERENCES

1. Landis, C., Hunt, W. A., Moe, S. K., and Visscher, M. B.: Color and Super Speed Cinematography of the Isolated Heart-Lung, Am. J. Physiol. 129: 400, 1940.

2. Kirch, E.: Pathogenese und Folgen der Dilatation und der Hypertrophie des Herzens, Klin. Wchnschr. **9**: 769, 1930.
3. Kountz, W. B., Gilson, A. S., and Smith, J. R.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations, AM. HEART J. **20**: 667, 1940.
Smith, J. R., Edwards, J. C., and Kountz, W. B.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations, AM. HEART J. **21**: 228, 1941.
4. Visscher, M. B.: The Restriction of Coronary Flow as a General Factor in Heart Disease, J. A. M. A. **113**: 988, 1939.
5. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, AM. HEART J. **20**: 399, 1940.
6. Brednow, W.: Die Formveränderungen des schlagenden Herzens, Ztschr. f. Kreislaufforsch. **27**: 401, 1935.
7. Strughold, H.: A Cinematographic Study of Systolic and Diastolic Heart Size, With Special Reference to Effects of Anoxemia, Am. J. Physiol. **94**: 641, 1930.

THE ELECTROCARDIOGRAM IN INDUCED FEVER

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BECAUSE minor electrocardiographic changes have been observed in many common febrile diseases,[1] and marked alterations noted in malaria, pneumonia, and typhoid fever,[2-4] similar changes might reasonably be expected with induced fever. However, the duration of natural fevers and their frequently nonremitting character are points of distinction from induced fever, and differences may therefore be expected in the respective electrocardiographic effects. For example, the prolonged auriculoventricular conduction time of natural malaria and the bradycardia of typhoid fever are uncommon in induced fever and may depend upon specific toxic effects of those infections.

Furthermore, although the effects of natural fevers upon cardiovascular physiology have been ascribed uncertainly to thermal, toxic, or mechanical factors, induced noninfectious fever affords an opportunity for critical evaluation of pure thermal change as it affects the pulse, blood pressure, cardiac output, blood flow, and electrocardiogram.[1, 5-11] Clinical and experimental studies of the electrocardiogram in fever have appeared in the literature.

Influence of Thermal Changes Upon the Electrocardiogram of Animals.—Stimulation of the hearts of animals by the application of heat or cold to the exposed organ has resulted in electrocardiograms characteristic of the areas so stimulated, and in a shortening by heat and a lengthening by cold of electrical systole and diastole.[12, 13]

In induced fever in animals, marked changes in the cardiac mechanism have been rare, though auriculoventricular block and ventricular rhythm have been described.[2] Negative P waves have become positive.[2] Shortening of the P-R[14] and R-T[9] intervals has been noted, and decrease in the amplitude of the QRS complex and notching of its deflections have been described.[2, 9] T waves have been increased in height or inverted.[4] Deepening of Q waves, disappearance of S waves, and S-T deviation from the isoelectric line have also been found. Some observers have noted changes which they were "accustomed to associate with coronary deficiency."[4] In general, however, the effect of induced fever upon the animal electrocardiogram is surprisingly insignificant, at least until critically high temperatures are reached.

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Furthermore, it is uncertain that these effects on animals, except those which follow the direct application of heat or cold, have been due entirely to thermal changes. For example, Cignolini has considered that the slight bradycardia and decreased systole noted in dogs during radio-induced fever may possibly be a specific effect of that form of energy upon the bundle of His and the adjacent sympathetic ganglia, independent of the heat induced.[5]

Influence of Fever Upon the Human Electrocardiogram.—The electrocardiographic effects of infectious, radio-induced, and diathermic hyperpyrexia have been studied in man. In general, these changes, also, have been of a relatively minor nature,[6, 9, 15] or have been considered within the permissible limits of variation from the normal.[7]

All changes have been proportional to the degree of fever induced, reaching a maximum at its height and receding with it, although with some lag. Neyman[16] has reported persistence of electrocardiographic changes for a few days after fever, but permanent alterations have rarely been found.[9]

The effects of malaria upon the electrocardiogram were studied by Mikawa, et al.,[6] and by Weicker, et al.,[11] in twenty-five cases of neurosyphilis. Of the latter group, all but five patients had moderate to severe hypertension, and nine showed radiographic evidence of aortitis. This may account, in part, for the author's conclusion that therapeutic malaria is more dangerous than other forms of induced fever. Fatal occlusion of a coronary artery occurred in one case during the fourth chill, and, in several others, there were minor T-wave changes to which "a coronary significance" was attached.

Alterations of the electrocardiogram during short-wave radiotherapy were observed in twenty-four normal subjects and six cardiac patients by Domenighini and Grigolo,[5] who used transthoracic radiation without permitting any rise in general body temperature. Alteration of skin conductivity caused by perspiration and peripheral vasodilatation was thus thought to be eliminated. No untoward reactions were observed, and it was concluded that at least some of the effects were due to a specific action of the radiation, apart from thermogenesis. However, the similar results obtained by Perinati (quoted by Domenighini[5]) with diathermy suggest that the common temperature increase may be more important than the particular form of energy employed.

Vesell and Bierman[9] reported in detail the electrocardiographic changes during radiotherapy and diathermy in ten cases in which a fever of 104° to 106.5° F. was maintained three to five hours; they were unable to infer that any cardiac damage had been induced. Details of their observations will be discussed later in comparison with the present study.

We have found in the literature to date no analysis of the electrocardiographic alterations in fever induced in the air-conditioned cabinet of Kettering, which would presumably afford a clear view of the effects of pure thermal change upon cardiac electrophysiology.

Mechanisms operating to produce electrocardiographic changes in fever may include alterations in blood and tissue pH caused by varying carbon-dioxide and lactic acid concentrations.[9] For example, alkalosis is at times encountered in fever therapy,[15] and this has been shown by Barber, et al.,[14] to be capable of producing deformity of the ventricular complex. Increase in metabolism and cardiac output, as well as peripheral vasodilatation[9] and hemoconcentration, may also affect the electrocardiogram. Many of the electrocardiographic alterations observed in induced hyperpyrexia have been ascribed simply to a change in the heart rate, for they have occurred also during sinus tachycardia after exertion.

Electrocardiographic Alterations Previously Described.—Changes in rhythm, aside from tachycardia, have been infrequently noted and have usually involved a shift from an abnormal prefebrile rhythm to a normal one. Weicker, et al.,[11] reported the elimination of auricular extrasystoles for eight days after induced fever; auricular fibrillation, however, was unaffected.

The P-R interval is usually shortened in artificial fever, and Weicker, et al.,[1] found in only one instance the increased duration reputedly common in natural malaria; Mikawa, et al.,[6] however, reported that the conduction time is generally prolonged after the chill.

An increase in the voltage of all component deflections of the electrocardiogram, and especially of the S wave, was also noted by Mikawa, et al. However, even though the S wave be considerably deepened, the sum of the R and S deflections has usually been found to be less during, than before, fever.[5, 9] To this observation Domenighini and Grigolo[5] attach an interesting interpretation. Considering the electrocardiogram as an index to the mechanics of cardiac action, they have assumed that a diminished sum of R and S in induced fever, without cardiac failure, signifies that the cardiac work has been accomplished by less than the previous expenditure of energy. This they attribute to improved coronary circulation or more efficient cardiac contraction, and upon these concepts they and Fianbaca explain their apparently favorable results after radiotherapy of the chest in angina pectoris.

T-wave alterations, variable in type and degree, have usually included a diminution in voltage. Weicker, et al.,[11] reported an instance in which a negative T_1, diphasic T_2 and isoelectric T_3 became upright during fever. T_3 has been the most labile portion of the electrocardiogram, in the experience of all investigators.

METHOD

Six men and fourteen women, whose ages averaged 42 years, between extremes of 21 and 57, received from one to nine inductions of fever in the air-conditioned Kettering cabinet. Fifty-two such treatments were observed, making an average of two and one-half treatments per patient; the mean duration was four and one-half hours, between limits of two and one-half and ten hours. The treatment

was for arthritis in nine instances, for taboparesis in three, for other forms of syphilis in six, and for gonorrhea in one. All of the patients had been carefully examined before the induction of fever, and those who had cardiovascular disease, beyond minor arrhythmia or moderate hypertension, were eliminated.

The maximum prefebrile blood pressure of the group was 182/116 mm. Hg, which changed during fever to 128/86 mm. Hg; this was accompanied by small S-T alterations, but not by subjective complaints. The average change in blood pressure in the entire group during fever was a decrease of 24 mm. Hg, systolic, and of 12 mm. Hg, diastolic. A return to the original levels occurred quickly in all cases after the cessation of fever.

Records were made with a string galvanometer, and in each instance the standard leads were taken before the induction of fever, during its rise, at its height, and upon its subsidence; additional tracings were taken in many instances. The electrodes were reapplied before each tracing, and the standardization was checked before each section. Notable changes in the electrical resistance of the patients were seldom encountered.

RESULTS

Changes in Rythm and Conduction.—Sinus tachycardia occurred in every instance; it was most marked during the induction of fever, with often a slight recession later, even though the fever had been maintained. As others have observed, the increase in heart rate was due principally to shortening of the T-P interval. In one case, recurrent ventricular escape was not observed after the first treatment; in another, multiple pacemakers disappeared during and immediately after fever, but later observations were not available. Numerous ventricular extrasystoles were eliminated in a third case during treatment, but returned later; this may have been due to a change in heart rate alone.

The P-R interval was usually found to be decreased in all leads by 0.02 to 0.04 second during fever; it returned rapidly to the original duration after the treatment, when it occasionally became 0.02 second longer than before fever. In every instance the original duration had been recovered before the next treatment. Similar observations were made by Vesell and Bierman,[9] in whose series the maximum decrease was 0.05 second during fever.

These authors reported that the P waves were diminished by 0.01 to 0.02 second in duration, with a maximum change of 0.04 second, and that the QRS complex was shortened by a maximum of 0.04 second, but remained unaltered in some instances and increased in a few. Similar observations were made in the present series.

In no instance was the QRS complex sufficiently prolonged to indicate a serious intraventricular conduction defect.

Vesell and Bierman[9] reported that the T wave was more often diminished than increased in duration, and that the ventricular, or R-T, section of the electrocardiogram in their series was shortened in all cases in Lead I, but increased in five of ten cases in Lead II or III, or both.

Such an analysis is rendered extremely difficult by the uncertainty of measurement and was not attempted in the present study.

Changes in Voltage.—Because of the fact that some patients received more treatments than others, changes in the deflections of the electrocardiograms were analyzed with respect to the number of cases in which they occurred, as well as to the number of treatments. This double analysis demonstrated that changes in any part of a tracing usually occurred consistently in all of the treatments of a given patient; there were, however, exceptions, particularly in the QRS complex and the T wave.

The P waves in all leads usually were increased in height during fever; the maximum increase was 2 mm., but some remained unchanged and a few became smaller. After fever, the deflection usually returned to its original height, and in several instances became even lower than before fever in Leads I and II; a post-febrile height greater than the original was commonly noted in Lead III. These observations are similar to those of Vesell and Bierman,[9] in whose series, however, a greater proportion of records showed diminished height during fever.

The same authors noted one instance in which Q_3 was sufficiently large during fever to fulfill the criteria for "prominent or significant Q_3," but the usual Q-wave changes in the present group were less than 1 mm., and diminution in height was more common than increase in Leads I and II. Q_3 was usually deeper after fever than before it, but with a maximum difference of 1 mm. A return to the prefebrile contour was usually prompt, but in one instance Q_2 remained larger during the period of observation than it had been before treatment.

The R waves of all leads usually decreased in height during fever, but they recovered promptly, and this often began late in the treatment and continued after it; at times they became higher than before fever. A compensatory decrease frequently occurred after the occasional early increase in the height of R_1. The maximum changes observed were 4 mm. in Lead I, 17 mm. in Lead II, and 7 mm. in Lead III. These alterations were not due to a change in the electrical axis; the latter appeared to be little affected by fever, as pointed out by Vesell and Bierman.[9]

These writers found that in several instances the height of the R deflection was less during fever than the normal minimum of 5 mm. but reported no slurring of the wave. The latter occurred in one case in the present series, and was associated with minor changes in the contour of the QRS complex and flattening of the T wave. During the next fever treatment of this patient, R_1 and R_2 were significantly slurred, and R_3 was completely obliterated. After both treatments the $S\text{-}T_2$ and $S\text{-}T_3$ segments remained slightly elevated temporarily, although the patient experienced no reaction suggestive of stenocardia. Later, fever did not produce such changes in this case. In the tracings

of another patient a slurred notch on the prefebrile S wave was displaced forward to a point near the apex of the R deflection during fever and moved back to its original position during recovery.

A deepening of S_1 occurred frequently during fever, but S_2 and S_3 were usually unaltered; the maximum change was 4 mm. in Lead III. Vesell and Bierman[9] reported increased depth of the S wave in Leads I and III, and equal numbers of increases and decreases in Lead II, with a maximum change of 4.5 mm. in Lead III.

R was added to S to permit comparison with the observations and interpretations of Domenighini and Grigolo, as noted above. RS_2 and RS_3 were generally decreased, as stated by these authors, but RS_1 was usually increased. The maximum diminution of R plus S was 10 mm. in Lead III. In all leads these changes were usually overcompensated later, especially after fever. Thus, granting for the moment that a decrease in R plus S is an indication of greater cardiac efficiency during fever, the overcompensation after subsidence of the fever would indicate that there is a dangerous phase of cardiac inefficiency after hyperpyrexia.

In the present series the S-T segments of all leads remained almost uniformly isoelectric, and all deviations were less than 1 mm. Vesell and Bierman[9] reported equally uniform depression of the S-T segment in Leads I and II and elevation in Lead III, but the changes were of the same order as in our cases.

The T wave in Lead I was usually decreased in height during fever, but later returned to, or exceeded, its original size. T_2 was increased and decreased equally often. T_3 was heightened by the majority of treatments, but decreased slightly in the majority of patients. The maximum changes were 3 mm. in T_1, 1 mm. in T_2, and 5.5 mm. in T_3. The observations of Vesell and Bierman[9] were not significantly different but included three instances in which a prefebrile inverted T wave in Lead III became upright during treatment. In our own group a change from plus 2 mm. to minus 3.5 mm. occurred once in Lead III, and less inversion was observed in four other instances. T_1 and T_2 were never found to be inverted during fever.

DISCUSSION

The present study adds to previous reports, especially that of Vesell and Bierman,[9] a detailed analysis of fifty-two electrocardiograms which were recorded on twenty patients during the induction of fever in the air-conditioned hypertherm of Kettering. The observations correspond closely with those of others on the human and animal electrocardiogram during fever and demonstrate the consistently minor nature of the electrocardiographic changes. The latter observation suggests that fever has only a slight direct influence upon the electrical activity of the heart

and that extracardiac factors are important in the production of the cardiovascular changes which occur in natural fever.

CONCLUSIONS

1. The electrocardiographic changes during hyperpyrexia, induced in the air-conditioned cabinet of Kettering, were observed through fifty-two treatments of twenty patients.

2. These changes were usually insignificant, and quickly disappeared when the fever subsided. In many instances, a temporary overcompensation occurred in the late febrile, or postfebrile, period. No permanent changes in the electrocardiogram were noted.

3. In no instance in the present series of patients, all of whom had normal hearts, were changes characteristic of coronary insufficiency observed, and no cardiac damage appeared to have resulted, insofar as the electrocardiogram and clinical observation permitted judgment.

4. In view of the close correspondence of the observations in the present series with those previously noted when fever was induced in other ways, it would appear that the observed changes are the result of physiologic processes incidental to the temperature increase, without regard to the mode of its induction.

REFERENCES

1. Cheer, S. N.: Effects of High Temperatures on Heart and Circulation, Am. J. Physiol. **84:** 587, 1928.
2. Browe, G. R.: The Heart in Typhoid Fever, Canad. M. A. J. **20:** 606, 1929.
3. Chagras, P.: Electrocardiographic Changes in Typhoid Fever, Compt. rend. Soc. de biol. **106:** 505, 1931.
4. Porter, W. B., and Bloom, N.: Heart in Typhoid Fever, AM. HEART J. **10:** 793, 1935.
5. Domenighini, R., and Grigolo, C.: Action of Short Waves Upon the Heart, Gior. med. d. Alto Adige **9:** 485, 1937.
6. Mikawa, T., Nemura, G., and Harada, N.: Electrocardiogram of Patients Inoculated With Malaria, Acta scholae med. univ. imp. in Kioto **11:** 391, 1929.
7. Phillips, J.: Physical Methods of Fever Production From a Physiologic Viewpoint, Arch. Phys. Therapy **19:** 473, 1939.
8. Roffo, A. E., and Taquini, A. C.: Electrocardiographic Changes Following the Application of Short Waves, Rev. Soc. argent. de biol. **10:** 190, 1934.
9. Vesell, H., and Bierman, W.: The Electrocardiogram in Fever; Changes in Induced Hyperpyrexia, Am. J. M. Sc. **191:** 484, 1936.
10. Wiggers, C. J., and Orias, O.: Circulatory Changes During Radiotherapy, Am. J. Physiol. **100:** 614, 1932.
11. Weicker, B., and Kessler, M.: Induced Malaria and the Electrocardiogram, Ztschr. f. Kreislaufforsch. **30:** 9, 1938.
12. Otto, H. L.: Action of Cold Upon T Waves of Electrocardiogram, J. Lab. & Clin. Med. **14:** 718, 1929.
13. Smith, F. M.: Effects of Heat and Cold on Ventricles and T-Deflection of Electrocardiogram, Heart **10:** 391, 1923.
14. Barker, P. S., Shrader, E. L., and Ronzoni, E.: Effects of Acidosis and Alkalosis on the Electrocardiogram, J. A. M. A. **106:** 324, 1936.
15. Simpson, W. M.: Studies in the Physiology of Fever, J. A. M. A. **106:** 246, 1936.
16. Neyman, C. A.: Artificial Fever Therapy, Springfield, Ill., 1938, Charles C Thomas, p. 44.
17. McGuigan, R. A.: Effect of Fever on Digitalis Action, J. Lab. & Clin. Med. **23:** 999, 1938.

MYOCARDIAL DEGENERATION WITH HYPERTROPHY AND FAILURE OF UNKNOWN CAUSE

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THE relationship of cardiac enlargement and heart failure to factors such as chronic valvular deformity and sustained hypertension, which require more work of the heart in order to maintain an adequate circulation, is well recognized. Although these causes for an increased cardiac load are present in a large percentage of patients with congestive heart failure, strain alone is not an entirely satisfactory explanation for the transition from compensation to decompensation without assuming some change in the status of the myocardium. This concept is not of recent origin, for William Stokes wrote, in 1854, "It was long ago observed by Laënnec that valvular diseases had but little influence on health when the muscular condition of the heart remained sound, and every day's experience confirms this observation." Many might consider this statement too dogmatic, but nevertheless would agree that the intrinsic integrity of the myocardium is the critical factor in cardiac function. Certainly, myocardial insufficiency occurs in the absence of valvular deformity or hypertension, and, even when causes for strain are existent, failure may be primarily due to depression of myocardial function by intoxications, infections, or metabolic disorders. Most often an inadequate coronary blood supply caused by coronary arteriosclerosis is responsible for the myocardial damage, although the possible noxious agents are numerous. It is frequently difficult to classify patients with myocardial insufficiency etiologically, and there is a tendency to assume, by exclusion, the presence of coronary arteriosclerosis in the absence of obvious causes for failure, particularly in middle-aged and older adults. Such reasoning will often give a correct diagnosis, but there is the inherent danger that the etiologic classification of coronary arteriosclerosis will be abused as much as the anatomic term, chronic myocarditis. It seems desirable to emphasize the possibility that cardiac enlargement and myocardial insufficiency may occur in the absence of the more common causes, and, in fact, in the absence of any discoverable cause. For this reason, and because of their interest, we have selected from 150

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autopsy examinations, made in the last two years, five cases in which there were degenerative changes in the myocardium without apparent cause. Four of the five patients were known to have syphilis, and the relation of this to the cardiac disease will be discussed.

REPORT OF CASES

CASE 1.—S. T. L., a 45-year-old negro barber, had been well until four years before admission to the hospital. As a young man he had been a professional athlete, and had continued to be very active until the onset of his illness. About April, 1935, he first noted fatigability and slight dyspnea on climbing steps. His weight gradually declined without obvious cause, and about eight months after the onset of symptoms he suddenly developed a severe attack of dyspnea, orthopnea, and cough, necessitating six weeks' confinement in bed. At that time he was told that he had "heart disease." He recovered from this acute attack, but the dyspnea on exertion became more incapacitating, and he entered a hospital about a year after the onset of symptoms. At that time he weighed only 170 pounds, which was forty pounds less than his previous weight. His heart was considerably enlarged, and there was evidence of pulmonary congestion. There were no murmurs or arrhythmia, and the blood pressure was 124/84. Electrocardiograms revealed a first-degree auriculoventricular block and intraventricular block. The blood cell count was normal except for 51 per cent lymphocytes in the differential leucocyte count. The blood Wassermann and Kahn reactions were negative, and the urine was normal. The patient remained ten weeks in the hospital and improved considerably on rest in bed and digitalis. After discharge his activity was limited, and he did fairly well for about three years, although climbing steps invariably caused breathlessness.

In the spring of 1939, however, exertional dyspnea became more severe, and, within a month, severe paroxysms of dyspnea, especially at night, forced the patient to come into the hospital again. He again showed evidences of pulmonary congestion, but no hepatic enlargement, ascites, or edema. The heart had increased in size; no murmurs were audible; the rhythm was normal; the sounds were distant; and the pulmonic second sound was louder than the aortic second sound. The blood pressure was 104/84. The electrocardiogram again showed first-degree auriculoventricular block and also left bundle branch block. The hemogram showed a persistent, relative lymphocytosis as high as 69 per cent.

The patient made very little improvement, and, since the shape of the heart suggested pericardial effusion with tamponade, paracentesis of the pericardium was undertaken. Only a small amount of bloody fluid was obtained. The patient's condition continued to become worse, and he died about four years after the onset of symptoms.

Autopsy.—The pericardium contained about 500 c.c. of unclotted fluid mixed with blood; the latter probably was the result of trauma to the heart during the paracentesis. The heart weighed 742 Gm., but the walls were stretched thin and cut with considerable resistance; the cut surface presented a grayish, glistening appearance. There were no gross lesions of the endocardium or valves, and no ante-mortem thrombus was present. The aorta retained its elasticity, was not dilated, and showed only a small amount of atheromatous change. No obstruction of the coronary ostia was present, and, except for scattered patches of intimal yellowing in the first part of the anterior descending artery, the coronary vessels were grossly normal. There was a hemorrhagic infarct in the lower lobe of the right lung which was of recent origin.

Histologic Examination.—The entire myocardium in the sections studied exhibited severe damage which became progressively more advanced from the epicardial to

the endocardial portions. Marked hypertrophy of the muscle fibers, with large distorted nuclei, many of which were granular or very basophilic, was evident in less seriously involved areas of the myocardium. The fibers themselves showed gradations of injury from hypochromatophilia, slight vacuolization, and transverse fracture, to complete disappearance. In large areas the muscle fibers appeared to have melted away, leaving a loosely packed interstitial tissue which contained only a few mononuclear cells and an occasional fibroblast. Even in portions in which muscle fibers remained, the interstitial spaces were very prominent, but contained only a scattering of lymphocytes and a rare eosinophile. Fibrosis was relatively limited throughout the sections.

The small blood vessels were engorged, and, in areas in which the muscle damage was most severe, small hemorrhages were seen in the interstitial tissues. In these locations in which the necrosis was severe, even the walls of the small blood vessels appeared vacuolated and disrupted.

Summary.—This patient exhibited evidences of cardiac enlargement and myocardial damage without hypertension, valvular disease, or evidence of coronary arteriosclerosis to account for the structural lesions. Myocardial insufficiency began four years before his death and was strikingly relieved for a period of approximately three years after bed rest and digitalization. The electrocardiograms showed intraventricular block on numerous occasions, which ultimately conformed to the left bundle branch pattern. The heart was hypertrophied and showed degenerative lesions without conspicuous cellular infiltration or fibrosis.

CASE 2.—J. T., a 43-year-old negro laborer, was first admitted to the hospital in 1937 for treatment of lobar pneumonia. He presented the classical signs of right upper lobe consolidation, and the acute phase of his illness terminated in seven days by crisis. During this examination no abnormality of the heart was noted; the size and shape were normal roentgenologically, and the blood pressure was 115/70. The blood Wassermann and Kahn reactions were strongly positive, and it was discovered that the patient had received antisyphilitic therapy in 1931. He remained in the hospital about two months, but further treatment of his syphilis was not considered advisable.

After his convalescence he worked as a delivery man for fourteen months, when he was again admitted to the hospital with congestive heart failure. One month previously, intramuscular injections of bismuth had been started, and, after the fourth treatment, he noticed the onset of cough, dyspnea on exertion, orthopnea, and edema of the ankles. At this time the heart was definitely enlarged; the rhythm was normal; the rate was 120; and there was a soft systolic murmur at the lower end of the sternum. The blood pressure was 128/104, and there were evidences of congestion in the lungs, liver, and lower extremities. Electrocardiograms showed left bundle branch block and ventricular premature contractions. The patient improved rapidly on rest in bed and digitalis, and was discharged from the hospital in five weeks.

In spite of greatly restricted activity, congestive heart failure promptly returned, so that hospitalization was required at the end of two months. The findings were essentially the same as on the previous admission. The blood pressure during the congestive stage was 124/96, but fell progressively with improvement to as low as 85/55. He again recovered promptly and was discharged after five weeks.

Upon return to his home, the dyspnea, orthopnea, and a "catching" pain about the left nipple soon required his readmission to the hospital. On this occasion his blood pressure was 114/90, the blood cell count was normal, the cardiothoracic ratio in the teleroentgenogram was 57 per cent, and the left bundle branch block was still manifest in the electrocardiogram. He again made a marked symptomatic

improvement which was repeated on three subsequent admissions until his eighth and final admission in May, 1940. At this time there were the usual signs of severe myocardial insufficiency, but he failed to respond to treatment and died about three months after admission.

Autopsy.—The heart weighed 510 Gm., and the left ventricle was greatly dilated. The wall of this chamber cut with some resistance, and at the apex there was an area of subendocardial fibrosis. All chambers contained "chicken-fat" clot. The valves were normal; there was no obstruction in the coronary arteries from the ostia to the smaller branches which admitted dissecting scissors. The aorta was not dilated, was normally elastic, and showed considerable atheromatosis in flat plaques, and also a moderate amount of longitudinal furrowing which suggested the possibility of syphilitic involvement.

Histologic Examination.—The muscle fibers were markedly hypertrophied, with very large, often pyknotic, nuclei. Areas with vacuolization, loss of striations, and transverse fracture were not uncommon, but the most profound damage was found in the subendocardium, where the degenerative changes were far advanced; the necrotic muscle was replaced in some areas by loosely packed connective tissue. There was very little cellular infiltration in the interstitial spaces, and only scattered small and large mononuclear leucocytes and fibroblasts were seen. None of these occurred in focal accumulations.

The small blood vessels in the muscle showed no encroachment upon their lumina, and the larger vessels in the epicardium were similarly unobstructed, although there was some thickening of the media. No perivascular cellular collections were seen in any of the sections, and small collections of lymphocytes in the subepicardium bore no relation to the blood vessels.

Summary.—This patient was first treated three years before his death for lobar pneumonia, at which time his heart was apparently normal. He was known to have syphilis, and his symptoms of myocardial insufficiency developed after the fourth of a series of intramuscular bismuth injections. He did not present any evidence of arterial hypertension or valvular disease, but there were marked cardiac enlargement, left bundle branch block, and myocardial insufficiency; from the latter he made unexpectedly good, although temporary, recoveries on six occasions over a period of sixteen months. The heart was hypertrophied, and showed areas of degeneration, particularly in the subendocardium.

CASE 3.—J. S., a 40-year-old white man, was admitted to the hospital Sept. 4, 1939, with congestive heart failure, and died thirty-six hours later. He had first been seen in an army hospital, in 1932, for the treatment of a penile lesion which contained spirochetes, as shown by dark-field examination. The extent of subsequent treatment is unknown. In July, 1934, he again received medical treatment because of an injured shoulder; at that time physical examination revealed no cardiac abnormality. The patient entered an army hospital in 1935, complaining of severe pharyngitis. The patient's heart was normal and the blood Wassermann and Kahn reactions were negative.

Early in April, 1937, the patient noted a dull, dragging sensation under the right costal margin. He entered a hospital, where he was found to have "cardiac enlargement and auricular fibrillation." No murmurs were audible, the Wassermann and Kahn reactions were still negative, and no etiologic diagnosis was made. The patient was discharged after one week.

Three months later he enrolled in the Civilian Conservation Corps, but developed "dyspnea on exertion and pain and tenderness in the region of the liver," for which he was admitted to the Walter Reed General Hospital Sept. 20, 1937. He was found to have the peripheral signs of moderate congestive heart failure, moderate cardiac enlargement, and auricular fibrillation. No murmurs were heard and

the blood pressure was 146/86. Flouroscopic examination revealed "left ventricular enlargement without aortic dilatation." The blood and spinal fluid gave negative reactions to tests for syphilis. The basal metabolic rate was normal.

On rest in bed and digitalis, improvement was marked, and he left the hospital Dec. 17, 1937, but was forced to enter a Veterans' Administration Facility ten days later because he again developed heart failure. On this admission the cardiothoracic ratio was reported as 50 per cent, and the blood pressure as 130/85. The electrocardiogram showed no abnormality other than auricular fibrillation. He was discharged from the hospital in a fair state of compensation two months later.

The patient was not hospitalized again until September, 1939, when he was admitted to this Facility with severe failure. He was comatose, orthopneic, and cyanotic; the cervical veins were engorged and pulsating; the heart beat was totally irregular, with a rate of 150. No murmurs were heard; the liver was enlarged; and there was edema of the superficial tissues in dependent portions of the body. Treatment was without avail, and death occurred thirty-six hours after the patient entered the hospital.

Autopsy.—The heart was greatly enlarged in all diameters and weighed 658 Gm. Although the chambers were large, the ventricular walls were thickened and showed no gross evidence of fibrosis or myomalacia. There was no appreciable dilatation of the aorta, which revealed only slight atheromatous change and nothing characteristic of syphilis. All of the valves were normal. The coronary ostia were patent, and the arteries showed only a slight degree of atheromatous change in the larger radicles, without any reduction of luminal cross section. Two wedge-shaped, healed infarcts were present in the right kidney.

Histologic Examination.—The muscle fibers were enlarged, and showed areas of light staining, hyalinization, loss of transverse striation, attenuation, and fragmentation. In sections cut transversely, considerable vacuolization was revealed. The nuclei were swollen and palely staining, with granular chromatin.

Spreading of the muscle bundles, and, to a lesser extent, of the fibers, was conspicuous, and the interstitial collagen was more compact. Cells were not prominent in the interfascicular tissues except for occasional areas of fibrosis between fractured fibers, in which leucocytes and fibroblasts were somewhat increased. The venous channels were engorged with blood, but the arterioles did not appear to be significantly damaged; the only change was an increase in perivascular connective tissue. Interstitial hemorrhage was present, and hemosiderin formation indicated that it had occurred ante mortem. The endocardium was undamaged except for an inflammatory reaction beneath a small ante-mortem thrombus.

Summary.—A 40-year-old man gave a history of recurring myocardial insufficiency over a period of 2.5 years. He had auricular fibrillation, which probably was not treated properly during periods between hospitalizations, but there was no clinical evidence of persistent arterial hypertension, valvular disease, or coronary artery involvement. Although serologic examinations for syphilis were repeatedly negative, there was a record of a penile lesion which had been diagnosed as syphilitic by dark-field examination. The heart was hypertrophied and showed degeneration, with some increase in fibrosis, particularly about the blood vessels.

CASE 4.—W. B. H., a 53-year-old white man, died in this hospital during his fifth admission for myocardial insufficiency. He had previously been treated in two other hospitals for the same disability, which, he stated, was first manifested about six years before his death. On one occasion, when he was 15 years of age, a "leaking valve" was discovered during the course of a routine examination, but this apparently had not caused him any difficulty during his army service or in pursuing his occupation as a mechanic and chauffeur. As a young man he had had gonorrhea and a penile lesion, associated with buboes, for which he was given a

course of antisyphilitic therapy in spite of the fact that syphilis was never definitely established as the cause of the lesion. The blood Wassermann and Kahn reactions were repeatedly negative in this hospital. He had been married twice; a stillborn child resulted from the first marriage, and the second was without issue.

When he first entered the hospital, in 1936, his complaints were of moderate exertional dyspnea, palpitation, and slight evening edema of the ankles, all of which had been noted in the preceding three years. There was no clinical evidence of congestion; the heart was somewhat enlarged, particularly in the region of the pulmonary conus. Auricular fibrillation, with a ventricular rate between 50 and 60 and a pulse deficit of 10 beats per minute, was noted. No murmurs were heard, and the blood pressure was 98/56. The blood cell count and urine sediment were normal.

At the end of one week the patient was sufficiently improved to leave the hospital, and was able to maintain his cardiac compensation fairly well on proper doses of digitalis for about eighteen months, when he again entered the hospital because of increasing dyspnea. At this time there were a few râles at the bases of the lungs, and a soft systolic murmur was heard in the third intercostal space to the left of the sternum. The auricles were still fibrillating; the blood pressure was 96/72; the cardiothoracic ratio was 55 per cent; and the blood Wassermann and Kahn reactions were negative. After ten days of rest in bed he was again discharged.

Within five months the patient was again hospitalized, and there was slightly more evidence of congestive failure. Auricular fibrillation was still present, and the cardiothoracic ratio was 60 per cent. Within two weeks he had recovered sufficiently to be discharged.

Five months later he began to expectorate bright red blood, and, on admission to the hospital, his condition was essentially the same as on previous occasions except that there was evidence clinically and roentgenologically of consolidation at the base of the right lung. This was interpreted as a pulmonary infarct. Examiners thought that both a systolic and diastolic murmur were audible at the apex of the heart during this admission. His condition responded well to treatment; the heart rate dropped to 80 per minute, and the blood pressure rose from 88/60 to 100/68, but dyspnea on slight exertion persisted. He was allowed to return home under a physician's care.

A little less than six months later he entered the hospital for the last time, with slightly more marked congestive failure than on previous occasions. The heart rate was very rapid, a soft systolic murmur, but no diastolic murmur, was heard, and the blood pressure was 88/56. Digitalis was administered, and, in the course of a week, his heart rate had decreased to 60. He was improving satisfactorily when he suddenly became cyanotic and dyspneic and died within a few minutes.

Autopsy.—The heart was enlarged in all diameters, and weighed 538 Gm. There was a small area of fibrous adhesions between the pericardial layers at the base of the pulmonary artery, without evidence of pericarditis elsewhere. The wall of the left ventricle was thickened, although both ventricles appeared to be dilated. No mural thrombi were attached to the endocardium, which was smooth and intact throughout. All of the valves were competent, and the mitral valve, in particular, showed only atheromatous change of the aortic leaflet, without any deformity. The aorta was not dilated in its first portion and showed only moderate atherosclerosis with calcification. In addition, there was longitudinal furrowing, without conspicuous whitening of the intima, which did not strongly suggest syphilitic aortitis grossly. The coronary ostia, however, were above the commissural line, and the posterior orifice was lipped, causing some decrease in its size. The coronary arteries down to the smaller branches showed only a minimal amount of atheromatous change and no decrease in their lumens.

Histologic Examination.—The epicardium was thin, and showed the usual amount of fat. In the subserous tissue there were several collections of plasma cells and small lymphocytes which were unrelated to blood vessels. The medium-sized coronary arteries showed some eccentric intimal thickening and vacuolization of the media, but little else, and the arterioles exhibited no damage.

The myocardium showed hypertrophy, atrophy, and degeneration. In a layer three or four fibers thick, immediately beneath the subserous fat, the parenchyma of the muscle was exceedingly granular, and much of it was lost. No nuclei were seen, and the fibers were widely spread, but no hemorrhage or cellular infiltration was present. From this outer layer to the subendocardial layers, the muscle showed hypertrophy with secondary atrophy, sarcolytic degeneration, and widespread transverse fracture. The striations were fairly well preserved. There was a reduction in the number of muscle nuclei, which showed no uniformity in size, shape, or staining qualities. In the subendocardium there was another layer of muscle resembling that beneath the epicardium, but the necrosis was more widespread and severe. Even the blood vessels in this region showed destruction of the adventitia and media in places, with irregular fibrosis. Throughout the myocardium the interstitial spaces were very prominent, apparently because of edema, because many clear spaces were visible. There was no interstitial hemorrhage or accumulation of cells, and surprisingly little fibrosis was present, even in the areas which were most severely damaged.

Grossly and microscopically, the kidneys showed no unusual changes except congestion.

Summary.—A 53-year-old man gave a history of progressive myocardial insufficiency over a period of six years; it was markedly improved by periods of hospitalization, but terminated in sudden and rather unexpected death. He had had auricular fibrillation for at least four years, and was very irregular in his use of digitalis when out of the hospital. Although there was a history of a genital lesion, the diagnosis of syphilis was not definitely established, and it was thought most probable before the autopsy that rheumatic mitral stenosis was the cause of his cardiac disease. No signs, however, were ever consistently elicited which would justify a diagnosis of mitral stenosis, and no other cause for the auricular fibrillation, cardiac enlargement, and myocardial insufficiency was found. The heart showed hypertrophy and degeneration which was most conspicuous beneath the epicardium and endocardium. There was no evidence of valvular disease.

CASE 5.—J. G., a 50-year-old negro farm hand, was first admitted to the hospital April 2, 1937. He had been well until two years previously, when, shortly after the onset of an upper respiratory infection, he was awakened from sleep by a severe attack of breathlessness, cough, and wheezing that lasted all night. The following day his physician called the patient's attention to the fact that his feet and ankles were swollen. After a month's rest in bed the patient returned to work, and was able to do heavy farm labor without difficulty.

One year later (1936), again in association with a cold, the patient's dyspnea and edema returned, but disappeared after six weeks in bed, and the patient was able to return to heavy work about the farm.

Four weeks before the patient entered the hospital, in 1937, cough, dyspnea, edema, and palpitation were again noted, but, despite rest in bed and digitalis, he became progressively worse. Physical examination revealed marked orthopnea and impairment of the percussion note and breath sounds, as well as crepitant inspiratory râles, at the bases of both lungs. The heart was enlarged; the beating was totally irregular, with an apical rate of 110 per minute; and the heart sounds were distant and of poor quality, with accentuation of the second sound at the pulmonic

area. A soft systolic murmur was heard in the mitral area, and a similar murmur was audible at the base. Ascites and marked peripheral edema were noted. The blood pressure was 158/86.

The blood cell count was normal; the urine showed traces of albumin and hyaline casts which disappeared as the patient improved. On three occasions the blood Wassermann and Kahn reactions were strongly positive. An electrocardiogram showed auricular fibrillation, with frequent ectopic ventricular contractions. The cardiothoracic ratio was 64 per cent.

The patient improved rapidly with rest in bed and the administration of digitalis, so that, within a month, the signs of congestion in the lungs and superficial tissues had disappeared, although the liver was still enlarged. The blood pressure had dropped to 116/66, and sinus rhythm, with occasional ventricular premature contractions, had been restored. There was, however, partial auriculoventricular block, with a P-R interval between 0.20 and 0.30 second, and, in the chest lead, the primary QRS deflection was downward. Improvement was continuous, and, at the end of two months, the patient was discharged entirely free of symptoms and without evidence of congestive failure, although the heart was considerably enlarged.

Six weeks later the patient suffered exposure during a rain storm while watching a ball game, and shortly thereafter had symptoms and signs of failure again, probably as the result of a respiratory infection and the exertion of hurrying home. On admission to the hospital at this time there was a pleural effusion on the right side, in addition to pulmonary congestion and edema of the legs. The heart rhythm was of sinus origin, with occasional ventricular premature contractions and an auriculoventricular conduction time at the upper limit of normal (0.20 second). There were no other definite abnormalities in the electrocardiogram except a low-voltage, W-shaped QRS complex in Lead I which was not prolonged. Again the patient improved rapidly, and in one month's time was allowed to leave the hospital.

Soon after returning home he was forced to assume the responsibilities of his family because of his wife's illness, and the previous symptoms of failure promptly returned. It became necessary for him to re-enter the hospital only twenty days after his discharge. At this time the situation was the same as before, with pulmonary congestion, edema, a large heart, sinus rhythm, a systolic murmur, and normal blood pressure. The auriculoventricular block previously noted was absent (P-R interval 0.16 second), but the voltage of the QRS complexes and T waves was low. The cardiothoracic ratio was 68 per cent, and the differential leucocyte count showed 42 per cent lymphocytes.

The patient improved gradually, but, during this stay in the hospital, electrocardiograms revealed a recurrence of the auriculoventricular block, at times with complete dissociation; in some instances the rhythm appeared to arise in the junctional tissues, for normal P waves could not be identified. Although this man's symptoms and signs were largely relieved, he was advised against leaving the hospital because his exertion was too great at home. The patient discharged himself, against advice, but within a month had to re-enter the hospital for the fourth time because of marked congestive failure. After two weeks of rest in bed, however, the symptoms were completely relieved, and all signs of congestion, except the enlargement of the liver, had disappeared. Electrocardiograms taken during this period showed variable rhythms and particularly marked depression of the sinus pacemaker, so that ventricular escape occurred. This apparently was not due to digitalis.

The patient was hospitalized in another institution for congestive heart failure about one month after leaving this Facility. He manifested the usual prompt improvement on the hospital regime, but quickly developed failure again at home,

and was admitted to this hospital for the last time in July, 1938. In spite of the severe failure the heart rate was only 62, and, in the electrocardiogram, no P waves could be recognized; the QRS complexes were of low voltage of supraventricular origin except for occasional ectopic ventricular beats.

This time the patient did not respond to treatment, and died about three years after the first onset of symptoms. A few days before death an area of consolidation was discovered in the mid-portion of the right lung; this was thought to be infarction or pneumonia.

Autopsy.—The heart was markedly enlarged in all diameters; it weighed 533 Gm., and the pericardial sac contained about 100 c.c. of deep-yellow-colored fluid. The ventricular walls were thin, firm, and seemed fibrous when cut. An ante-mortem thrombus was enmeshed in the columnae carneae of the left ventricle.

The aortic valve cusps were not deformed, but the commissures were somewhat widened and the margins adjacent to the aorta slightly bound down, so that the valve pocket was smaller than usual. Although a water test was not done, it was assumed that this valve was competent, for a diastolic murmur was never heard, and the valve cusps seemed adequate to close the orifice, which was not widened. The other valves were normal.

The aorta in its first part was dilated and relatively inelastic. The surface was roughened by raised atheromatous plaques, furrowing, and an occasional, depressed, whitish scar suggestive of syphilitic aortitis. There was no obstruction of the coronary ostia, and the arteries showed only a minimal amount of flat atheromatous change, without any obstruction.

In the right kidney there were two areas of healed infarction, and in the upper lobe of the right lung there was a recent hemorrhagic infarct.

Histologic Examination.—The muscle fibers were for the most part enlarged, but many showed secondary atrophy, necrosis, and fibrous tissue replacement. The striations were distinct, although many of the enlarged fibers stained poorly and were vacuolated and fractured. The muscle nuclei were enlarged, with blunted ends. Interstitial spaces were prominent, and the entire connective tissue supporting structure of the heart was accentuated. Throughout the ventricular wall there were small, localized areas of muscle damage and fibrosis in which only a few scattered erythrocytes were seen; leucocytes, plasma cells, and fibroblasts were conspicuously scarce. In the older areas of damage, fibrosis was complete, and this was particularly true in the subendocardium, where the damage had been most severe.

The larger coronary arteries showed some intimal thickening which did not significantly encroach upon the lumens, and the smaller vessels were thin walled, with a slight increase of perivascular connective tissue, but no other cellular elements.

Beneath the partially organized thrombus on the endocardial surface there was a definite leucocytic and fibroblastic infiltration.

Summary.—A 50-year-old negro farm laborer had eight attacks of myocardial insufficiency, with congestion, in the three years before his death. These began originally with an attack simulating bronchial asthma, but subsequent events did not seem to confirm the original impression that the heart failure was primarily the result of pulmonary hypertension. None of the other common causes of heart strain, such as arterial hypertension and valvular disease, were present to account for the marked cardiac enlargement and myocardial insufficiency. It was thought that this case might be one of syphilitic myocarditis, although the surprising recuperative power of the heart seemed incompatible with the usual conceptions of this disease. The heart was enlarged, and there were areas of muscle damage and fibrosis throughout the myocardium.

COMMENT

These five patients were men between the ages of 40 and 53 years. Two were white and three were negroes, but, in proportion to their representation in the hospital population, the preponderance of colored patients in this group is more than three to two. The clinical manifestations were varied, although all had recurring attacks of congestive heart failure over periods lasting from 22 months to 6 years. Three had auricular fibrillation at some time during their illness, and one had it consistently; two showed the characteristic pattern of left bundle branch block (new nomenclature) in their electrocardiograms, and two had partial auriculoventricular block. A relative and absolute increase in the number of lymphocytes and large mononuclear cells was noted in the differential leucocyte counts of two patients, and in two of the five cases a pulmonary infarct was diagnosed, one before death and the other at autopsy.

These patients are grouped together, however, because each exhibited cardiac enlargement, with myocardial damage and insufficiency, for which no adequate cause could be found. At autopsy no congenital defects, dynamically significant valvular deformities, or coronary occlusions were demonstrated, and the moderate elevation of the diastolic blood pressure exhibited by some during periods of failure was not considered evidence of a chronic hypertensive state. In the past[1] it has often been assumed that, when cardiac hypertrophy is found at autopsy, it is due to arterial hypertension, providing other causes are not apparent, and even when evidence is lacking that the blood pressure was ever elevated. Our patients did not have more than moderate elevation of their diastolic pressures during their illnesses, and this returned to levels below the usually accepted upper limits of normal when compensation was regained. Furthermore, none of these patients had any significant degree of the renal arteriolar sclerosis or arteriosclerosis which is observed[2] in a high percentage of cases of persistent arterial hypertension of sufficient severity to cause heart failure and death. Cardiac hypertrophy and congestive failure, in the absence of hypertension or any obvious cause, have also been reported by others.[3] None of our patients presented any clinical signs or symptoms suggestive of hyperthyroidism, severe anemia, metabolic disorders, or avitaminosis, and the pathologic examinations failed to reveal any definite clues as to etiology. Hypertrophy of the ventricles, as indicated by increased heart weight and enlargement of the muscle fibers, was present in all cases, and apparently occurred in the absence of the usual factors that increase the load against which the heart must work. Since sections from both ventricles were not routinely studied, it cannot be stated, except in one case, that both the right and left ventricles were hypertrophied. In addition to the hypertrophy, a widening of the tissue spaces was generally con-

spicuous and was perhaps due to interstitial edema. These spaces were usually clear, occasionally with some increase in the density of the ground substance; less commonly they contained a loose fibrillar network. There was some increase in perivascular fibrosis, but very little interstitial fibrosis except in one case, in which it was both diffuse and extensive in the walls of all chambers. For the most part the severely damaged portions of the myocardium showed little fibrosis.

In the sections studied, cellular infiltration was not prominent. There were a few clusters of cells not related to blood vessels in the epicardium of several hearts; there were collections of small round cells beneath ante-mortem thrombi on the endocardium in two cases and about a blood vessel in another, but otherwise only scattered, small groups of mononuclear leucocytes, plasma cells, and fibroblasts were seen. Two hearts showed areas of interstitial hemorrhage and collections of hemosiderin pigment which were easily accounted for by the damaged arterioles.

The most important microscopic change observed in all cases was degeneration of the muscle, which, however, varied considerably from heart to heart in character, extent, and severity. In four of the five cases the most marked damage was in the subendocardial region, although it was not limited to this area. In one case there was a layer of necrosis beneath the endocardium and a similar one beneath the epicardium, but the muscle between was little involved. There were areas of damage throughout the muscle of all four chambers of one heart, whereas in others there were small, localized patches of necrosis, in addition to the more extensive subendocardial damage. The damaged muscle fibers were usually palely staining and retained their striations, although the transverse ones were frequently difficult to see. Cross fragmentation, sometimes with fibrosis between the opposing ends, was common, and in these cases the process appeared to represent a "melting," for the distribution of sarcoplasm was uniform to the point of fracture. In some sections the muscle fibers were granular, and in others there was a loss of sarcoplasm, producing a moth-eaten appearance. This even involved the media of the arterioles in three cases, so that the architecture of the wall was destroyed but the lumen was not encroached upon. In only one case was the lumen of a small coronary artery obstructed, and this probably was the result rather than the cause of the degenerative process in the muscle, for the latter extended far beyond the distribution of this particular vessel.

These pathologic changes were interpreted as primarily degenerative in character, rather than inflammatory, because the usual cellular infiltration of inflammation was not predominant. The terms "interstitial," "isolated," "diffuse," and "primary" myocarditis have been used[4-6] to describe the lesions (cellular infiltration) encountered in the hearts of patients who died from heart failure without obvious cause.

Although the changes observed in our cases do not justify the diagnosis of myocarditis, there was considerable similarity between the clinical course of our patients and that described for those with myocarditis. Others[7] have reported "nonsuppurative myocardial degeneration with dilatation and hypertrophy" in children, and "idiopathic myocardial degeneration"[8] in the puerperal period, with descriptions of myocardial damage which more closely approximates the observations in our cases. These authors were unable to suggest a satisfactory explanation for the pathologic changes, but, unlike their patients, four of ours gave a history or had serologic evidence of syphilis, with suggestive changes in the aorta which did not affect the coronary ostia or aortic valve enough to account for the myocardial damage. The fifth patient was a negro who gave no history of infection, treatment, or a positive serologic reaction. Although the spinal fluid was not examined, the aorta was not grossly involved and, therefore, no definite evidence of syphilis was found in this case. The possibility that syphilis was responsible for the cardiac manifestations in these cases cannot be dismissed, however, even though the ability of the *Treponema pallidum* to attack the myocardium directly, except in the production of gummatous lesions, has never been decisively proved. In the earlier stages of syphilitic cardiovascular disease, manifested only by aortitis, it is not uncommon for the patient to complain of symptoms suggesting myocardial insufficiency, frequently without pain referred to the heart. This is difficult to explain as a result of aortic involvement alone, even if some degree of coronary ostia occlusion is assumed, and modern textbooks[9-10] admit the possibility that syphilitic myocarditis may occur, but consider it a rare phenomenon. Certainly the clinical criteria for the diagnosis are vague, and the final conclusion in such cases has been reached partly by exclusion of other causes. Hamman and Rich[11] and Magill[12] reported what they considered to be cases of syphilitic myocarditis, characterized by a history or serologic evidence of syphilis, cardiac enlargement, and myocardial insufficiency, without any of the usual causes associated with these manifestations. Their diagnoses depended to some extent upon histologic evidence, although they were not able to demonstrate spirochetes in the tissue or isolate them by the injection of macerated muscle into a rabbit's testicle. The pathologic criteria are uncertain, however, for there is little agreement as to the microscopic appearance of nongummatous syphilitic myocardial involvement.[13-17] Warthin's[18, 19] demonstration of spirochetes in the myocardium in many cases of syphilis has never been successfully repeated, and the other diagnostic criteria, such as interstitial edema, focal accumulations of round cells, and fibrosis, have been observed by us, as well as by others,[14] in cases of myocardial insufficiency when syphilis played no part. Therefore, the fact that the pathologic process in our cases seemed to us to be more degenerative

than inflammatory would not necessarily exclude syphilis as the causative factor. No other etiology was suggested by long clinical observation and pathologic study, although it should be emphasized that the syndrome and even the pathologic changes might easily have been ascribed to coronary arteriosclerosis, employing the usual criteria, if it had not been known that the coronary arteries were not obstructed in any way.

The five cases reported here represent only a small percentage of all patients with cardiac disease, but it is our impression that this group might be easily enlarged by the inclusion of other patients, particularly negroes with syphilis who present evidence of cardiac enlargement and myocardial damage and insufficiency, without apparent adequate cause. The proof that syphilis is of etiologic importance in these instances, however, awaits the development of more exact criteria.

SUMMARY

Five cases of fatal heart failure, with necropsy, are reported.

All of the patients showed cardiac hypertrophy and myocardial degeneration, without evidence of hypertension, valvular disease, coronary artery disease, or any of the less common causes of these structural changes.

Four of the five patients presented suggestive evidence of syphilis in the history, serologic reaction, or aorta, and the possible etiologic relationship of this disease to the myocardial lesions is discussed.

REFERENCES

1. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. **5**: 939, 1928.
2. Kaplan, B. I., Clark, E., and de la Chapelle, C. E.: A Study of Myocardial Hypertrophy of Uncertain Etiology, Associated With Congestive Heart Failure, AM. HEART J. **15**: 582, 1938.
3. Levy, R. L., and Rousselot, L. M.: Cardiac Hypertrophy of Unknown Etiology in Young Adults. A Clinical and Pathological Study, AM. HEART J. **9**: 178, 1933.
4. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, AM. HEART J. **5**: 129, 1929.
5. De la Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis, Arch. Int. Med. **47**: 942, 1931.
6. Hansmann, G. H., and Shenken, J. R.: Acute Isolated Myocarditis, AM. HEART J. **15**: 749, 1938.
7. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infant and Young Children With Myocardial Degeneration and Fibrosis (So-Called Congenital Idiopathic Hypertrophy) Am. J. Dis. Child. **45**: 828, 1933.
8. Gouley, B. A., McMillan, T. M., and Bellet, S.: Idiopathic Myocardial Degeneration Associated With Pregnancy and Especially the Puerperium, Am. J. M. Sc. **194**: 185, 1937.
9. White, Paul D.: Heart Disease, ed. 2, New York, 1937, Macmillan Co., p. 274.
10. Levine, Samuel A.: Clinical Heart Disease, Philadelphia, 1936, W. B. Saunders Co., p. 181.
11. Hamman, L., and Rich, A. R.: A Case of Syphilitic Myocarditis, Internat. Clin. **4**: 221, 1934.
12. Magill, T. P.: Syphilitic Myocarditis, Bull. Johns Hopkins Hosp. **57**: 22, 1935.
13. Boyd, W.: Acute Myocardial Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **14**: 35, 1930.

14. Saphir, Otto: Syphilitic Myocarditis, Arch. Path. **13**: 226, 436, 1932.
15. Brooks, H.: The Heart in Syphilis, Am. J. M. Sc. **146**: 513, 1913.
16. Brooks, H., and Carroll, J. H.: The Symptoms and Diagnosis of Involvement of the Heart in Syphilis, New York State J. Med. **13**: 328, 1913.
17. Norris, J. C.: Syphilis of the Myocardium and Coronary Arteries, J. A. M. A. **108**: 169, 1937.
18. Warthin, A. S.: The Persistence of Active Lesions and Spirochetes in Tissues of Clinically Inactive or "Cured" Syphilis, Am. J. M. Sc. **152**: 508, 1916.
19. Warthin, A. S.: Primary Tissue Lesion in the Heart Produced by Spirocheta Pallida, Am. J. M. Sc. **147**: 667, 1914.

A SYNDROME DUE TO OCCLUSION OF ALL ARTERIES ARISING FROM THE AORTIC ARCH

Report of a Case Featured by Primary Thrombocytosis and Autohemagglutination

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COMPLETE absence of pulsations in all arteries of the upper extremities and neck is extremely unusual. We take this opportunity to report such a case, in which bilateral cataracts, proliferative retinitis, and atrophic rhinitis were complications. Other unusual abnormalities were thrombocytosis and autohemagglutination.

CASE REPORT

U. C. H. No. U61721 was a Spanish woman, aged 29 years.

First Entry.—July 30, 1940, to Sept. 14, 1940.

Present Illness.—Four years before entry the patient suddenly collapsed and fell to the floor; following this she became progressively weakened. Her hands and feet felt cold and at times were blue. She suffered from palpitation and a transient substernal ache brought on by slight exertion. She became dizzy on arising quickly from the supine position. Her memory was markedly impaired for both recent and remote events, and she suffered from emotional instability. Her vision became blurred because of gradually developing cataracts. In December, 1938, a cataract was removed from the right eye without restoration of vision, and from November, 1939, she had been totally blind.

The past history and family history were noncontributory. The patient had never used tobacco or alcohol and had not taken dinitrophenol. There was no history of syphilis. Four children were living and well, aged 9 years, 7 years, 5 years, and 2 months, respectively. One miscarriage (twins) occurred shortly before the onset of the present illness.

Additional history obtained from physicians who had previously attended the patient revealed that between February and June, 1931, a number of blood pressure readings in the arms varied between 120/70 and 136/80. In July, 1937, the blood pressure in the arms was 100/60. In November, 1938, no blood pressure measurements could be obtained in either arm, and the radial pulses were not palpable. The blood pressure in the legs was 160 to 170, systolic, with indefinite diastolic readings. Oscillometric readings were zero in both arms, 6 in the left thigh, and 4 in the right thigh. A strong pulsation was present in the suprasternal notch. The carotid pulse was palpated on the right, but not on the left. A loud to-and-fro murmur, transmitted into the neck, was heard over the left sterno-clavicular region, left supraclavicular area, and left second intercostal space. Roentgenograms of the chest showed nothing abnormal except rudimentary seventh cervical ribs. A scalenectomy and resection of the left cervical rib, which were done January 13,

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1939, revealed a fibrosed subclavian vein crossing the first rib, medial to the scalenus anticus tendon; the subclavian artery was not seen. In December, 1938, examination of the ocular fundi revealed a meshwork of new blood vessels growing over both discs. The temporal half of the right lens was opaque, and the patient was not able to count fingers with this eye at a distance of more than 1 foot. Vision in the left eye was 20/40. A cataract was removed from the right eye without restoration of vision. Laboratory examination at that time revealed that the basal metabolic rate was −12 per cent, the serum calcium, 9.5 mg. per cent, the serum phosphorus, 3.35 mg. per cent, the urea clearance, 62 per cent, the venous pressure (antecubital vein), 10 cm. of water, and that the arm-to-tongue and arm-to-lung circulation times were 16.5 and 8.5 sec., respectively.

Physical Examination.—The patient was a well-developed, poorly nourished woman. The skin was warm and dry. The lymph nodes were not enlarged. The extraocular movements were normal. The pupils were dilated and irregular, and did not react to light or in accommodation. The bulbar conjunctivae were markedly injected. Slit-lamp examination of the conjunctivae showed clumps of erythrocytes traveling as units in the larger vessels; the normal differential ratio of flow of blood constituents (from center to periphery of vessel) was not present; the small venules and capillaries contained columns of blood cells in rouleaux. Ophthalmoscopic examination (right eye): linear incisional scar of the cornea; optic nerve head atrophic, margins blurred, irregular, and without perceptible elevation or depression; many arterioles occluded and obliterated and some bloodless (ghost-vessels); large areas of retinal hemorrhage; macula not seen. A dense cataract prevented seeing the left fundus. Light and color perception was intact, but light projection was questionable in all but the nasal field of the left eye. There was faint perception of light in the right eye. The nasal mucous membrane was crusted, and there was a large perforation of the septum. Marked periodontoclasia was present. The tonsils were atrophic. The thyroid was not enlarged. There was marked pulsation of the vessels in the suprasternal notch. The chest, breasts, and lungs were normal. The left half of the diaphragm was elevated 6 cm. above the right. The area of cardiac dullness extended 6 cm. to the left of the midsternal line in the fifth intercostal space; the heart sounds were loud and snapping; the rhythm was normal and the rate was 102 per minute; a soft, blowing, systolic murmur was heard at the apex, and another was localized over the aortic area; there were no thrills; the aortic second sound was louder than the pulmonic second. The abdomen, extremities, and nervous system were normal. Psychiatric examination disclosed impaired memory for recent and past events. Examination of the peripheral vascular system showed no unusual color or thermal changes. The carotid, subclavian, brachial, radial, ulnar, and intercostal arteries were not palpable or pulsatile. The pulsations in the abdominal aorta and arteries of the lower extremities were normal. No collateral circulation was visible over the chest or shoulder girdle. The blood pressure was not obtainable in the arms; in the left leg it was 160/100; in the right leg, 140/100.[1] The oscillometric readings were zero in both arms, 4 in the right lower leg, and 3.5 in the left lower leg. The venous pressure was not increased. There were very few visible or palpable superficial veins. Tests for reactive hyperemia in both arms were normal. There was neither excessive blanching on elevation of the limbs nor cyanosis in the dependent position.

Laboratory Data.—Hemoglobin was 9.6 Gm., or 70 per cent; erythrocyte count, 4,400,000; leucocyte count, 8,900; P.M.N., 42 per cent (filaments 40 per cent, nonfilaments 2 per cent); lymphocytes, 40 per cent; monocytes, 18 per cent.

Platelet count (Rees and Ecker): 10 platelet counts during the six weeks' observation varied between 1,200,000 and 1,500,000.

Packed cell volume was 35.

Sedimentation rate (Linzenmeier) was 14 minutes.

Auto-agglutination of erythrocytes occurred at body, room, and icebox temperature.

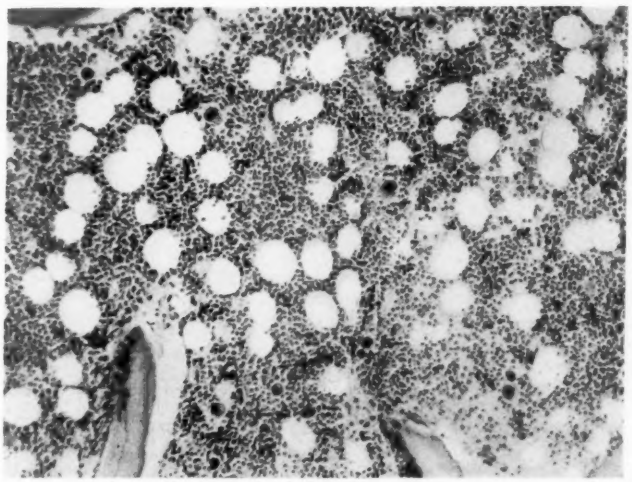

Fig. 1.—Sternal bone marrow biopsy, demonstrating increased numbers of megakaryocytes (×120, hematoxylin and eosin stain).

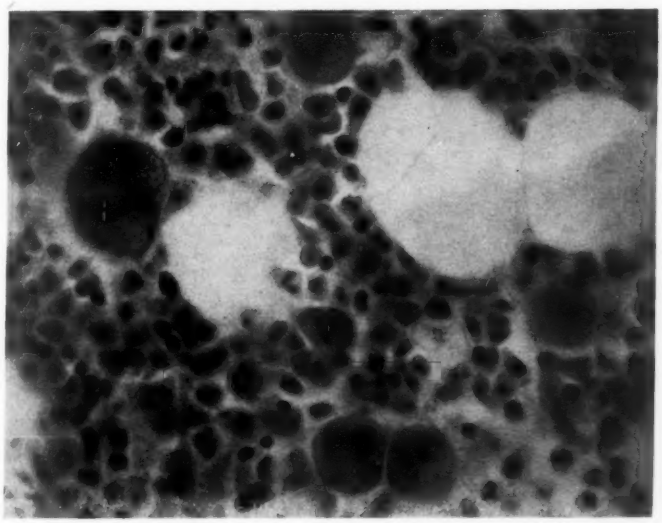

Fig. 2.—High power magnification (×700) of sternal bone marrow biopsy, demonstrating megakaryocytes and active erythropoiesis (hematoxylin and eosin stain).

Sternal biopsy (Figs. 1 and 2): Hyperplasia of both myeloid and erythropoietic series was observed. Megakaryocytes were normal in appearance, but increased in number (one to five per oil-immersion field). Eosinophiles were present in great numbers. There was an excessive number of platelets on the smear of the material obtained by sternal puncture. Intact megakaryocytes were infrequent, but many large agminations of nuclear material, surrounded by masses of adherent thrombocytes, were present. These tended to form "streamers" during the course of making smear preparations (Figs. 3, 4, and 5).

Capillary fragility (Dalldorf) was slightly increased.
Plasma ascorbic acid was 0.19 mg. per cent.
Bleeding time (Ivy) was 3 minutes.
Coagulation time (Lee and White) was 8 minutes.
Recalcified plasma coagulation time[2] was 90 seconds.

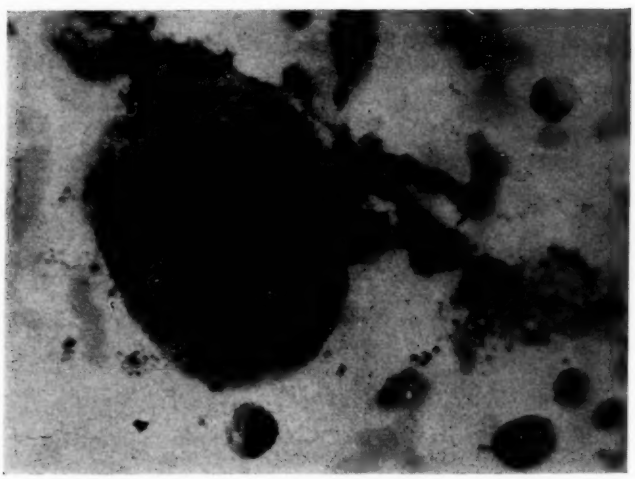

Fig. 3.—Smear preparation demonstrating megakaryocyte obtained by sternal bone marrow puncture (×700, Giemsa stain).

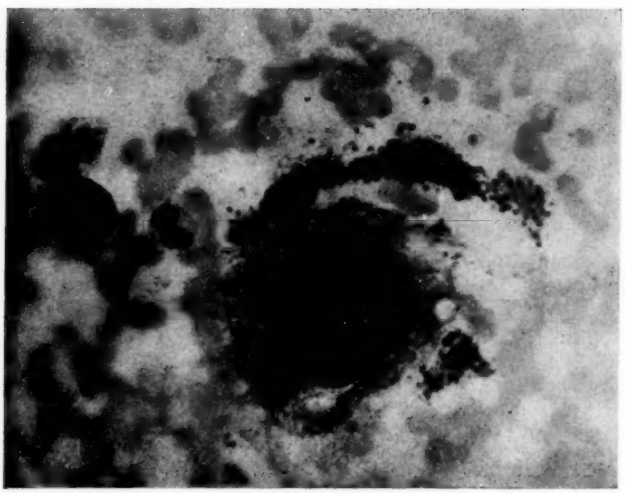

Fig. 4.—Smear preparation demonstrating megakaryocyte obtained by sternal bone marrow puncture (×700, Giemsa stain).

Prothrombin concentration (Quick) was 110 per cent.
Clot retraction was normal.
Urinalysis, P.S.P. excretion, Mosenthal, Diodrast clearance tests,* and intravenous pyelograms were normal.
Stool was normal.
Serum calcium was 10.85 mg. per cent.

*The authors are indebted to Dr. Meyer Friedman for this determination.

Serum phosphorus was 5.20 mg. per cent.

Serum proteins: Total, 8.00 per cent; albumin, 4.21 per cent; globulin, 3.79 per cent.

Circulation time (Decholin) was 15.5 sec.

Kolmer and Kahn tests were negative.

Electrocardiogram showed sinoauricular tachycardia. Rate was 106. T_1 was diphasic; T_2, inverted; T_4, notched and low.

Skin temperatures over the entire body were essentially normal.

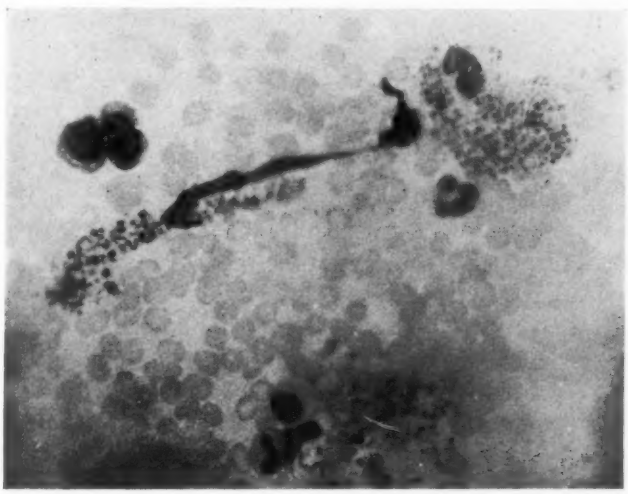

Fig. 5.—Smear preparation demonstrating agminations of platelets obtained by sternal puncture (×700, Giemsa stain).

Biopsy.—Histologic examination of sections of an artery 2 mm. in diameter, situated in the usual location of the right brachial artery, and of sections from the right pectoral, biceps, and gastrocnemius muscles revealed normal striated muscle and normal appearing, thin-walled arterioles and venules.

Roentgenologic Examinations: Chest (including fluoroscopy).—A cervical rib was present on the right side. There was a small fragment of bone in the region from which the left cervical rib had been removed. There were no abnormal aortic pulsations. The heart and great vessel shadows were within normal limits. The left half of the diaphragm was elevated and moved physiologically, but with a lag. *Abdomen.*—The spleen appeared to be of normal size. *Skeletal system.*—The bony density was essentially normal. There was a slight alteration of the trabecular pattern of the ileum and of the inferior articular process of the second lumbar vertebra. There were a few minor cystic changes in the greater tuberosity of the right humerus and in the neck of the left femur. The vascular markings of the skull were prominent symmetrically. The joint surfaces and joint spaces were normal.

Second Entry.—Feb. 26, 1941, to March 8, 1941.

During the intervening six months the patient had noted increasing weakness, frequent headaches, and occasional nervous spells. Her nose had become tender, and two weeks before entry the bridge had collapsed, producing a saddle deformity. All of her upper teeth had been removed. Her general condition was essentially as before, except that she appeared to be more weakened. There was marked crusting of the mucous membrane in both nares. There was a mature cataract in the left eye. The right eye showed an old retinitis proliferans, with new-formed

vessels and partial detachment of the retina. The presence of hemorrhages signified that the process was still active. Examination of the heart was of interest in that the murmurs which had been previously heard were now inaudible. There was a marked increase in the amount of hair on the legs.

Diodrast cardiograms, done according to the Robb-Steinberg technique, revealed no abnormalities of the heart or aorta. Spinal fluid examination showed that Kolmer was negative; colloidal gold, 0012210000; protein, 43.1 mg. per cent; cell count, 3 lymphocytes. Infrared photographs revealed no increase in venous circulation. Two platelet counts were 820,000 and 890,000, respectively.

REVIEW OF PREVIOUS CASES

Five cases of complete absence of pulsations in the carotid arteries and in the arteries of both upper extremities have been reported; in all of them the loss of pulsation was presumably due to syphilitic involvement of the transverse arch of the aorta (Table I). There are striking similarities in the symptomatology in these cases and the case herein reported. In all cases, the pulsations in the vessels of the lower extremities were normal. There were evidences of circulatory insufficiency in the arms in only one case.[7] The central nervous system symptoms included headaches, vertigo, syncope, emotional instability, delirium, loss of memory, aphasia, and hemiplegia. Vertigo and syncope were frequently brought on by arising quickly from the supine position. Ocular manifestations included photophobia, choroiditis, cataracts, and proliferative retinitis. The subject of this report had, in addition, atrophic rhinitis. It seems probable that the essential pathologic process was similar in all of the cases reviewed, i.e., occlusion of the large vessels arising from the arch of the aorta.

Eden[8] has recently reviewed the literature dealing with the vascular complications arising from cervical and abnormal first thoracic ribs. Those patients who had absence of the radial pulse showed evidences of circulatory insufficiency in the affected arm. In a few, the pulsations returned after removal of the cervical rib. In no instance were both radial pulses absent, and never were abnormalities of the carotid pulse observed. Although cervical ribs were present bilaterally in our case, they did not appear to be the cause of the vascular abnormalities.

Absence of pulsation in the carotid arteries and in the arteries of the arms has occasionally been noted in cases of dissecting aneurysm of the aorta.[9] However, such a diagnosis was considered untenable in this case because there was no history of chest pain, dyspnea, or hypertension, and there were no evidences of circulatory insufficiency in the arms.

Nygaard and Brown[10] have described "essential thrombophilia" as a condition occurring in previously healthy subjects, characterized by sudden, widespread occlusion of major arteries and veins, with marked signs of circulatory insufficiency often resulting in gangrene, and with insignificant histopathologic changes in the involved vessels. They observed variations in the plasma coagulation time in some of their pa-

tients. In the one case in which the platelet count was significantly elevated, no histopathologic examination of the tissues was performed, so that it cannot be classified as a proved case of "essential thrombophilia." It is apparent that our patient's disease did not resemble this condition. The constant thrombocytosis and the absence of any demonstrable cause of the vascular occlusions suggested the possibility that our patient was suffering from an obscure thrombotic process due to accelerated and pathologic coagulation of the blood. An increase in the number of platelets in the circulating blood, occurring as a primary disease,[11-13] is an extremely rare condition, although secondary thrombocytosis is not uncommon in myeloid leucemia, polycythemia, megakaryocytic leucemia, and after splenectomy.[14] Among the reported cases of primary thrombocytosis, in that of Epstein, et al.,[11, 15] there was atrophy of the spleen, and, in that of Uotila,[12] marked leucocytosis and, at times, polycythemia. In one of the two cases reported by Rowlands and Vaizey,[13] the spleen was enlarged to the level of the umbilicus and slight polycythemia was present. In the subject of our report, no condition known to be associated with a secondary elevation of the platelet count was found to be present. There was a moderate increase in the megakaryocytes of the sternal bone marrow, and in the smear of the material obtained by sternal puncture there were a few intact megakaryocytes and many large agminations of nuclear material surrounded by masses of adherent thrombocytes. The spleen was not palpable, and roentgenologically it was found to be of normal size. Aside from the increased platelet count, no abnormalities in the bleeding and clotting mechanism of this patient were demonstrated.

A further investigation of the coagulative potency of the plasma was performed in the following manner. Nine cubic centimeters of blood were withdrawn from the antecubital vein, mixed quickly with 1 c.c. of a 1.34 per cent solution of sodium oxalate in a test tube, and centrifugalized at 2,000 r.p.m. for 10 minutes. Varying amounts of the supernatant plasma were pipetted into 13 by 100 mm. glass tubes, and placed in a water bath at 37° C. Two cubic centimeters of blood obtained from the antecubital vein of a patient with hemophilia (whole blood coagulation time, 50 minutes) were added to each of these tubes and the coagulation time measured to the nearest half minute. The results are given in Table II. It can be seen readily that there was no significant difference in the ability of this plasma and normal plasma to accelerate the coagulation of hemophilic blood.

Among the many factors which favor the agglutination of platelets, and hence influence the occurrence of thrombosis, is to be included an increase in the concentration of the weakly electronegative proteins, i.e., fibrinogen and globulin. Autohemagglutination, associated with hyperglobulinemia, is often found in patients with multiple myeloma.

TABLE I

PREVIOUSLY REPORTED CASES OF COMPLETE ABSENCE OF PULSATION OF ARTERIES ARISING FROM AORTIC ARCH

AUTHOR	AGE	SEX	SYMPTOMS	SIGNS	PATHOLOGIC CHANGES
Shikhare[3]	Middle aged	M	Vertigo, photophobia, and periods of syncope	All arteries of upper half of body non-pulsatile	Autopsy: Fusiform aneurysm of ascending and transverse aorta. Lumina of large vessels arising from arch occluded by ante-mortem thrombus, which had propagated from large clot in aortic arch
Crawford[4]	52	M	Occipital headaches, pain in back of neck, dyspnea, vertigo, cough, and tingling of left thumb. Radial pulse noted to have been absent 6 weeks previously	Radial, brachial, and external carotid pulsations absent. Systolic blood pressure in legs, 125 mm. Hg	Flouroscopy: Aneurysm of arch and descending aorta
Kampmeier and Neumann[5]	35	M	Recurrent periods of vertigo and syncope, particularly on arising from supine position. Left radial pulse noted to have been absent 2 years previously	Radial, brachial, and carotid pulsations absent. Visible and palpable systolic pulsations at angle of left scapula. B.P. in legs, 178/110	Fluoroscopy: Aneurysm of ascending and transverse aorta
Cohen and Davie[6]	60	M	Onset of symptoms 12 years previously, accompanied by cataract of left eye. Headache, attacks of syncope, delirium, and cardiac failure	Radial and carotid pulsations absent. Numerous small pulsating subcutaneous vessels over chest and upper abdomen. Systolic blood pressure in arms, 40 to 50 mm. Hg, in legs, 210 mm. Hg. Marked retinal arteriosclerosis of right eye. Left eye obscured by cataract	Autopsy: Fusiform aneurysm of ascending and transverse aorta. Orifices of all vessels arising from arch obliterated

TABLE I—CONT'D

AUTHOR	AGE	SEX	SYMPTOMS	SIGNS	PATHOLOGIC CHANGES
Maurer[7]	33	F	Right hemiplegia 3.5 years previously, followed by complete aphasia and numerous periods of syncope, and weakness brought on particularly by sitting upright and relieved by lying down	Skin over shoulder girdle, upper extremities, head, and neck less warm than rest of body. Lips and nail beds cyanotic. No pulsations in carotids or arteries of upper extremity. Arms and hands atrophic. Systolic B.P. in legs, 120 mm. Hg	Autopsy: Saccular aneurysm of transverse arch of aorta. Arch filled with laminated clot with thrombotic extensions completely occluding innominate, left common carotid, and left subclavian artery

TABLE II

AMOUNT OF HEMOPHILIC BLOOD (C.C.)	AMOUNT OF PLASMA (C.C.)	COAGULATION TIME	
		WITH PATIENT'S PLASMA (MIN.)	WITH NORMAL CONTROL PLASMA (MIN.)
2	0.01	26	24
2	0.05	10	8
2	0.10	5.5	5.5

However, thrombosis is an unusual occurrence in this disease. Wintrobe and Buell[16] found two such reports in the literature, and added a third. Their patient had thrombosis of the retinal veins and symptoms suggesting Raynaud's disease. McCombs and McElroy[17] reported an instance of autohemagglutination due to a cold-agglutinin in a patient with peripheral vascular symptoms. In our case, the globulin content of the serum was only slightly increased. Marked agmination of the erythrocytes was observed in the small blood vessels in the conjunctiva. Autohemagglutination due to a pseudo-agglutinin was observed in vitro. Roentgenologic examination of the entire skeleton revealed no evidence of myeloma. The plasma cells were not increased in the sternal bone marrow.

Because of the localization of the occlusive process to the large vessels arising from the arch of the aorta, it seems unlikely that changes in the blood plasma or an increase in the number of circulating blood platelets could have been entirely responsible for this condition. The etiology in our patient therefore remains obscure.

SUMMARY

A syndrome due to occlusion of all of the vessels arising from the arch of the aorta has been described, and a case reported. The condition is characterized by complete absence of pulsations in the carotid arteries

and in the arteries of both upper extremities. The following may be present: (1) central nervous system symptoms, including headaches, vertigo, syncope, emotional instability, delirium, loss of memory, aphasia, and hemiplegia; (2) ocular manifestations, including photophobia, choroiditis, cataracts, and proliferative retinitis; (3) atrophic rhinitis; and (4) atrophy of the arms and hands.

Although syphilis was presumed to be the etiologic agent in the previously reported cases, no evidence of its presence could be found in this case. The exact etiology is unknown, although thrombocytosis and autohemagglutination may have been contributing factors.

REFERENCES

1. Standardization of Blood Pressure Readings, AM. HEART J. **18**: 45, 1939.
2. Aggeler, P. M., and Lucia, S. P.: The Potency of Blood Coagulating Substances, Am. J. M. Sc. **199**: 181, 1940.
3. Shikhare, P. V.: Notes on a Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, Indian J. Med. **2**: 326, 1921.
4. Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, J. A. M. A. **65**: 1395, 1921.
5. Kampmeier, R. H., and Neumann, V. F.: Bilateral Absence of Pulse in the Arms and Neck in Aortic Aneurysm, Arch. Int. Med. **45**: 513, 1930.
6. Cohen, H., and Davie, T. B.: Bilateral Obliteration of the Radial and Carotid Pulses in Aortic Aneurysm, Lancet **1**: 582, 1933.
7. Maurer, E.: Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysms of the Aortic Arch, AM. HEART J. **17**: 716, 1939.
8. Eden, K. C.: The Vascular Complications of the Cervical Ribs and First Thoracic Rib Abnormalities, Brit. J. Surg. **27**: 111, 1939.
9. Shennan, T. N.: Dissecting Aneurysms, Medical Research Council Special Report Series No. 193, 1934.
10. Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia, Arch. Int. Med. **59**: 82, 1937.
11. Epstein, E., and Kretz, J.: Über einen Fall von hochgradiger Thrombocytenvermehrung, Klin. Wchnschr. **9**: 1177, 1930.
12. Uotila, U.: On Hemorrhagic Thrombocythemia, Acta med. Scandinav. **95**: 136, 1938.
13. Rowlands, R. A., and Vaizey, J. M.: Primary Thrombocythaemia, Lancet **2**: 1217, 1938.
14. Tocantins, L. M.: The Mammalian Blood Platelets in Health and Disease, Medicine **17**: 2, 155, 1938.
15. Epstein, E., and Goedel, A.: Hämorrhagische Thrombocythämie bei vasculärer Schrumpfmilz, Virchows Arch. f. path. Anat. **292**: 233, 1934.
16. Wintrobe, M. M., and Buell, M. V.: Hyperproteinemia Associated With Multiple Myeloma, Bull. Johns Hopkins Hosp. **52**: 156, 1933.
17. McCombs, R. P., and McElroy, J. S.: Reversible Autohemagglutination With Peripheral Vascular Symptoms, Arch. Int. Med. **59**: 107, 1937.

Department of Clinical Reports

PASSAGE OF A HOLLOW NEEDLE INTO THE VENOUS BLOOD STREAM TO THE HEART, THROUGH THE CARDIAC WALL, AND INTO THE THORAX

Report of a Case

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THIS report is one of a case in which a needle which was being used for an intravenous injection became separated from the hub and entered the blood stream.

The circumstances were as follows: A physician was giving an injection into the left cephalic vein of a 45-year-old white man on May 28, 1938. Upon completion of the injection he applied pressure at the point of puncture with a small pledget of cotton, in order to avoid leakage, and attempted to withdraw the needle. Only the hub of the needle, however, remained attached to the syringe. Diligent search of the surrounding tissue failed to locate the lost part of the needle. The patient did not complain of pain or other symptoms. Roentgenograms of the arm and chest, taken the same day, failed to show the needle. However, the patient was observed at frequent intervals thereafter, and, on June 24, 1938, about one month after the injection, a posteroanterior roentgenogram of the chest revealed a linear shadow, the dimensions of which corresponded exactly to those of the lost needle. The needle was lying horizontally at the level of the eighth thoracic vertebra (Fig. 1). Fluoroscopic examination showed that the needle lay outside the heart, and appeared to be embedded in the prepericardial fat between the inferior surface of the apex of the heart and the left dome of the diaphragm.

The patient has not had any complaint referable to the circulation, heart, lungs, or pleura. Roentgenographic and fluoroscopic examination of the chest on July 7, 1938, showed that the shadow was in the same location. Four subsequent examinations, the last on March 27, 1940, revealed no alteration in the position of the needle.

The electrocardiograms were normal. The blood pressure has been constantly 120/80. The heart rate has averaged 76 per minute, and the

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rhythm has been normal. Cardiac murmurs have never been heard, and the size of the heart has remained normal. At present the patient is active and works as a commercial artist, which is his usual occupation.

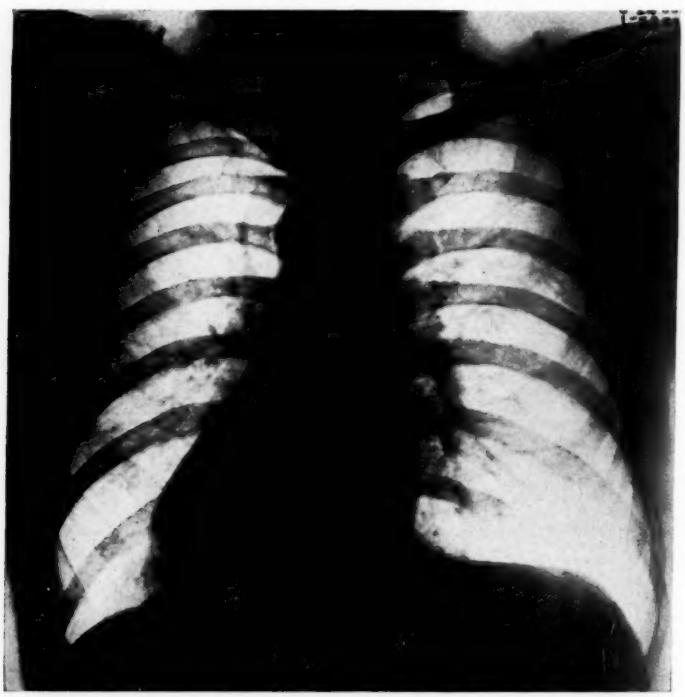

Fig. 1.—The arrows point to the needle shadow between the inferior surface of the heart and the left dome of the diaphragm.

DISCUSSION

From its location in the chest, it is apparent that the needle must have entered the heart, passed through its wall, and lodged in the silent area where it now rests. The course of the needle after it entered the venous blood stream must have been through the left cephalic vein, axillary vein, subclavian vein (up to this point all of the veins possess valves), innominate vein, superior vena cava, and, finally, the right side of the heart.

There are three pathways by which foreign bodies may enter the heart. The first, and most common, is directly through the chest wall, as in the case of gunshot wounds or the thrust of a sharp instrument. Examples of these abound in the literature.[1-4]

The second pathway is through tissue from a distant part of the body; the foreign body is forced by muscular contraction along a more or less circuitous route, possibly by following paths of least resistance, until by chance it eventually reaches the thorax and the heart. It is probable that only a sharp instrument, such as a nail or needle, can

perform this feat. A striking example of this was reported by Rea and Hoover;[5] a needle entered the foot of a patient when he accidentally stepped upon it, and four years later he died as the result of thoracic disease induced by the passage of the needle through the pleura and pericardium. At autopsy the needle was found lodged in the heart.

The third pathway is illustrated by the case reported in this paper. Another remarkable instance of the same route was reported by Blaha.[6] In his case a soft rubber catheter was introduced into a gravid uterus to induce an abortion, and, when the uterus expelled its contents, the catheter was not among them. The patient became infected and died. At autopsy the catheter, 24 cm. long and 4 mm. in diameter, was found lying in a channel formed by the inferior vena cava, the right auricle, the superior vena cava, the left innominate vein, and the internal jugular vein. This case and the one described in this paper illustrate how relatively large bodies may gain entrance into the venous blood stream and be carried to the heart.

The importance of investigating the flexibility and sturdiness of each needle before use, especially for intravenous injections, is emphasized by the present report. It should be realized that the needle consists of two parts, namely, a flexible cannula and a rigid hub, and that the junction of these two parts is the weak spot in the construction of every needle. It is consequently important (when administering any injection) not to introduce the needle more than three-fourths of its length, so that, if it should accidentally become separated from the hub, it might still be possible to grasp its free end before it becomes completely submerged in the tissues.

SUMMARY

1. A case is reported in which a hollow needle entered the venous blood stream, was carried to the heart, penetrated its wall, and came eventually to lie in the prepericardial fat between the heart and the diaphragm, without producing any untoward symptoms.

2. The pathways by which foreign bodies may enter the heart are described.

3. The hazard described in this paper, although a rare one, warrants the recommendation that the flexibility and sturdiness of needles be carefully tested before they are put to intravenous use.

The author is grateful to Dr. A. S. Hartstein and Dr. B. Kurz, of New York City, for permitting him to examine their records of this case.

REFERENCES

1. Bland-Sutton, Sir John: A Lecture on Missiles as Emboli, Lancet 1: 773, 1919.
2. Cope, Z.: Extraction of Sewing Needle From the Heart, Lancet 1: 813, 1920.

3. Goldberger, H. A., and Clark, H. E.: Migration of Needle into Heart Through Chest Wall: Surgical Removal, Electrocardiographic and Roentgenographic Studies, J. A. M. A. **105**: 193, 1935.
4. Fair, George L.: Foreign Body in the Heart: Report of a Case With Retention of a Large Needle With Recovery, New York State J. Med. **35**: 453, 1935.
5. Rea, Charles, and Hoover, P. A.: An Unusual Case of a Needle Found in the Heart at Necropsy, J. A. M. A. **109**: 266, 1937.
6. Blaha, J.: Embolische Verschleppung eines Fremdkörpers (Gummikatheter) ins Herz bei einem kriminellen Abortus, Zentralbl. f. Gynäk. **59**: 746, 1935.

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Department of Reviews and Abstracts

Selected Abstracts

Eyster, J. A. E., and Meek, W. J.: The Sequence of Fractionate Contraction at Different Surface Regions on the Right Auricle and Ventricles of the Dog's Heart. Am. J. Physiol. **134**: 513, 1941.

The sequence of occurrence of fractionate contraction at the different surface regions of the right auricle and ventricles of the dog's heart is determined by recording differential potential-time curves from the various regions along with a constant reference curve. The results are indicated in the accompanying figure.

The fact that no criterion is available at present which can be used to determine the instant of "excitation" of a region of heart muscle, is brought out and discussed.

AUTHORS.

Frey, J.: Experimental Observations on the Effects of Hydrostatic Forces on the Circulation. Arch. f. Kreislaufforsch. **7**: 329, 1940.

This is an extensive investigation on the effect of posture upon the circulation in animals, healthy subjects and cardiac patients with and without congestive heart failure. Among the principal conclusions are the following.

In animals the assumption of a semisupine position from a supine one causes a temporary 30 per cent decrease in venous flow of the hindleg and a more protracted 10 per cent increase in arterial flow, a 2 per cent increase in flow in intestinal vessels, a 5 per cent decrease in flow in the forelimb vessels, no effect on flow in brain vessels, a 10 per cent decrease in cardiac output, a 10 per cent rise in mean blood pressure and heart rate. Following histamine the results are different in these animals, viz.: The same change in position causes a 60 per cent decrease in venous flow of the hindleg and a 25 per cent *decrease* in arterial flow, a 20 per cent *decrease* in flow in intestinal vessels, a 15 per cent decrease in flow through brain vessels, a 35 per cent decrease in flow through forelimb vessels, a 50 per cent decrease in minute output of heart, a 30 per cent *decrease* in mean blood pressure, and a 30 per cent increase in pulse rate. Extensive studies on man are to be found in the monograph. The author concludes that the use of the semireclining posture *with legs dependent* acts as a bloodless venesection, and this improves the circulation of the failing heart.

KATZ.

Graybiel, A.: A Consideration of the Effects of Oxygen Lack on the Cardiovascular System From the Viewpoint of Aviation. J. Aviation Med. **12**: 183, 1941.

The degree of anoxia intentionally encountered under present flying conditions in civil and military aviation does not damage the normal heart. The changes observed in the electrocardiogram do not indicate heart injury; they are probably due in part to the alkalosis resulting from overventilation.

Heart failure of the congestive or anginal type has been produced in patients with severe degrees of heart disease on exposure to oxygen tensions simulating altitudes of 14,000 to 20,000 feet or higher.

In a total of 7 million passengers carried by five major airlines only three deaths occurred aloft; the cause in each case was ascribed to heart failure. Of five deaths known to have occurred shortly after the passengers deplaned, two were the result of heart failure. Information in regard to lesser attacks of heart failure is inadequate, but there is good reason for believing such instances are not numerous.

The general rule that "if you can walk, you may fly" has proved satisfactory in practice. Passengers with well-compensated heart disease need not hesitate to fly at the highest altitudes now flown in commercial aviation provided that an additional supply of oxygen is used. However, patients with severe valvular disease, with easily provoked angina pectoris, or who have recently had congestive failure, as well as those who are old and feeble, might well be advised against traveling by air.

AUTHOR.

Gross, F., and Matthes, K.: Venous Pressure in Man. Arch. f. Kreislaufforsch. 8: 175, 1941.

Venous pressure was recorded optically. The venous pulse of the cubital vein followed the arterial except for notching at the time the jugular pulse collapsed. This may be due to direct impact or to open arteriovenous anastomoses. Respiratory fluctuations also were present due to variations in venous flow to the heart. Marked variations in venous pressure as in Valsalva experiments were associated with variations in blood content of the skin (as measured with transillumination recorder and photoelectric cell).

KATZ.

Dressler, M., and Moskowitz, S. N.: Fetal Electrocardiography and Stethography. Am. J. Obst. & Gynec. 41: 775, 1941.

Forty gravidas were studied routinely in the last two months of pregnancy, to determine the diagnostic significance of the fetal electrocardiogram and the fetal stethogram, separately and simultaneously, in evaluating the presence of a viable fetus. The individual value of each method was enhanced by the combined study.

The fetal stethogram was positive in 100 per cent of the cases; the fetal electrocardiogram, in 80 per cent.

The stethogram is helpful in studying the rate, rhythm, and regularity of fetal heart sounds, the systolic and diastolic phases, murmurs, the uterine souffle, and fetal movements. The intensity of the fetal heart sounds depends upon the site at which the microphone is applied and upon maternal and fetal conditions. In most cases the second sound is louder than the first. As a rule, diastole is longer than systole, but in the presence of fetal tachycardia they may become equal.

The electrocardiogram is valuable in the presence of positive tracings. The absolute diagnosis of fetal presentation is made by the fetal electrocardiogram. If the waves are negative, a vertex presentation is present; if positive, a breech presentation is present. In the presence of an equal systolic and diastolic phase, the first sound is recognized by its relationship to the R-wave of the fetal electrocardiogram.

AUTHORS.

Bayer, O., and Wasmuht, K.: The Duration of the Q-T Interval in Absolute Arrhythmia. Arch. f. Kreislaufforsch. 7: 309, 1940.

The duration of electrical systole was measured in fifty-eight cases of myocardial disease with grossly irregular rhythm. In only nine instances was the duration of systole outside the expected range, and in only four of these was there no explanation for the lengthening. This study confirmed the constancy of the relationship of electrical systole to heart rate. This relationship is unchanged when the irregular heart action changes to a regular sinus rhythm. The most important factor determining electrical systole is thus the heart cycle duration.

KATZ.

Dungern, M.: Alterations in Duration of Isometric Contraction, Ejection Time, Systole and Q-T Interval. Arch. f. Kreislaufforsch. 8: 52, 1941.

After moderate exercise, the relative durations of electrical (Q-T) and mechanical (first to second sound) are shortened. (The use of the maximum amplitude of the first heart sound as the time at which ejection begins which the author employs is not always an accurate criterion. L. N. K.)

After injection of Ca intravenously in therapeutic amounts, a slowing of rate and relative shortening of mechanical systole which is not so marked as the shortening of electrical systole occur.

KATZ.

Wendt, L.: S-T Depression as a Sign of Anaerobic Cardiac Metabolism. Arch. f. Kreislaufforsch. 8: 74, 1941.

Anoxemia and insulin can cause an S-T depression. Stimulation of the vagus also causes an S-T depression. S-T depression is considered to indicate a decrease in the potential energy of the heart with a decrease in oxidative and an increase in the anaerobic metabolism. (This is a lengthy, polemical discussion.)

KATZ.

Albers, D., and Bedbur, W.: Physiological Variations in the Duration of the Ventricular Electrocardiogram. Arch. f. Kreislaufforsch. 8: 150, 1941.

This is an analysis of the literature, and 2,000 electrocardiograms of the author's were used in the study. The author considers that Q-T duration equals, on the average, $3.75 \sqrt{\text{cycle length}}$. $\text{QRS} = 0.92 \sqrt{\text{cycle length}}$. S-T (from end of QRS to end of T) $= 2.83 \sqrt{\text{cycle length}}$. S-T lengthens with age, the factor being 0.004 (age—45).

KATZ.

Stroud, W. D., and Wagner, J. A.: Silent or Atypical Coronary Occlusion. Ann. Int. Med. 15: 25, 1941.

The explanation of painless infarction is difficult. Possibly the symptoms which patients experience, such as swallowing, choking, gagging or dyspnea, may be pain equivalents. Possibly the nerve supply about the coronary vessels is different; or are they members of the hyposensitive group described by Libman?

From a therapeutic standpoint, it seems to be extremely important to be cognizant of the possibility of coronary occlusion and myocardial infarction in the absence of pain. Vagus symptoms of weakness, etc., in patients with hypertension or the onset of increased dyspnea, together with progressive failure in patients with previous mild failure, should make one alert to this serious condition. Putting the patient to bed and checking with serial electrocardiograms seem highly desirable.

The corollary may be equally true. Any patients with the typical pain of coronary insufficiency but no other suggestive clinical findings, even in the absence of changing T-waves in the electrocardiograms, must be considered as possible cases of coronary occlusion without myocardial infarction and treated accordingly. This means total bed rest for a week or ten days as a myocardial infarction might be developing. In these instances, clinical judgment is of much more importance than the electrocardiograms.

AUTHORS.

Laufer, S. T.: Subacute Myocardial Infarction or Necrosis. Canad. M. A. J. 45: 236, 1941.

Myocardial necrosis without typical symptoms or an acute onset, which can be detected by delayed electrocardiographic changes of coronary occlusion type, is described as a clinical entity under the title of subacute myocardial infarction or necrosis.

The mechanism of its production and the clinical symptoms and signs, justifying it as an entity, are discussed. The symptoms are so atypical that the patient often continues his regular activities, to his own detriment.

The delayed appearance of electrocardiographic changes are in accord with the clinical picture and may be discovered only accidentally some time later.

The importance of a careful history in aiding the detection of cases of subacute myocardial infarction or necrosis is strongly stressed.

A raised leucocyte count may be the only positive sign in the cases outlined.

AUTHOR.

Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus. Arch. Path. 32: 569, 1941.

Disseminated lupus erythematosus is founded morphologically on a well-defined series of alterations of the collagenous tissues. The characteristic organic changes, previously considered as heterogeneous, can now be understood as local manifestations of the widespread damage of collagen. Various concepts of lupus erythematosus as a disease with predominant localization in a single organ or as a diffuse disease of the peripheral circulation can be entertained no longer.

AUTHORS.

Gorenberg, H., and McCleary, J.: Rheumatic Heart Disease in Pregnancy. Am. J. Obst. & Gynec. 41: 45, 1941.

Three hundred forty-five cases of pregnancy complicated by rheumatic heart disease are reported.

Seventy-seven cardiac failures occurred in this group, an incidence of 22.3 per cent. It is possible to foretell fairly accurately which patient with heart disease will fail unless adequate bed rest is enforced. Several prognostic aids are offered.

The functional capacity of the heart in the nonpregnant state is of great importance, 83 per cent of the failures occurring in the badly incapacitated groups, 2B and 3, while only 17 per cent of the failures were in the comparatively well-functioning Classes 1 and 2A.

An equally important aid is the patient's age; 42.6 per cent of the pregnancies in women over 30 years of age were complicated by cardiac failure as compared to 16.1 per cent in the group under 30.

A third significant aid in prognosis is the presence or absence of a history of previous failure. Of those that decompensated before, 75 per cent had cardiac failure when pregnant as compared to a 14.1 per cent incidence of cardiac failure in the previously compensated group.

The authors feel, therefore, that the patient whose measure of functional capacity places her in the relatively severe grades of heart disease, the cardiac patient who is more than 30 years of age, the cardiac patient who gives a history of previous decompensation, should be willing, if she wishes to assume the burden of pregnancy, to submit to frequent antenatal observations from the very beginning of her pregnancy and she must be willing and able to spend the greater part of the pregnancy at absolute bed rest if necessary. The number of pregnancies borne by women with rheumatic heart disease, in itself, is apparently of no consequence. The multigravid, however, will more commonly fall into one or more of the three groups mentioned above.

The incidence of cardiac failure in pregnancy can be reduced markedly if the general principle of early and absolute bed rest is followed. The authors had two failures in their last 103 cases, and one of those was possibly preventable.

Eighty per cent of the seventy-seven cardiac failures that were seen at this hospital occurred before the last month of gestation. Acute failure during labor is a rarity. Clinical experience follows very closely the physiologic changes which indicate that pregnancy exerts a steadily increasing circulatory burden, beginning when the pregnancy begins and reaching a maximum during the eighth month. A lightening of this circulatory load occurs during the period four to six weeks preceding delivery with a consequent clinical improvement. Therefore, it is unwise to resort to late pregnancy terminations and follow the general rule of allowing the gestation to go to term.

Each pregnancy presents an individual problem in the management of labor. In this series, 8.4 per cent of the patients were delivered by the abdominal route and 91.5 per cent were delivered vaginally. Since the incidence of morbidity, as expressed by fever with its concomitant elevation in pulse rate, and the mortality rate are significantly higher following cesarean section, and since cardiac decompensation is a rare accident during labor, the "burden of proof" lies with cesarean section. This consideration applies only to section for the cardiac condition per se. Patients who have had the benefit of treatment and go into labor well compensated may in general be handled on the basis of obstetric indication, essentially as though not suffering from heart disease.

AUTHORS.

Hannesson, H.: Tuberculosis of the Pericardium and Heart. Tubercle 22: 79, 1941.

Involvement of the pericardium by a contiguous or neighboring tuberculosis is not so rare as is generally supposed. Tuberculosis limited to the pericardium is rare. Invasion of the pericardium from tuberculosis of the pleura, mediastinum, or thoracic vertebrae is observed from time to time. In miliary tuberculosis tubercles may be demonstrated in the myocardium at autopsy although their presence cannot be detected clinically.

Tuberculosis of the pericardium is usually a fatal disease, but, in the event that the tuberculous process in the pericardium and elsewhere in the body subsides, the mechanical effects on the heart are a result of pericardial healing. The inflammatory process heals with resulting cohesion of the visceral and parietal layers of the pericardium, so that partial or complete obliteration of the sac occurs. This condition imposes extra work on the heart and results in cardiac hypertrophy and in some cases in ultimate heart failure.

If the pericarditis is extensive and particularly if there is an associated mediastinitis, the resulting fibrosis may greatly hamper the right auricle and the great veins, particularly the inferior vena cava, so that the return of blood to the

heart is partially obstructed. This results in congestion of the liver, which becomes chronic and causes recurrent ascites. This condition is called chronic mediastino-pericarditic pseudocirrhosis of the liver or Pick's disease.

Post-mortem statistics indicate that probably no serious disease is so frequently overlooked as one that affects the pericardium. Tuberculosis of the pericardium is not a rare condition. The terms anatomically primary and clinically primary tuberculous pericarditis are unsatisfactory. The occurrence of anatomically primary tuberculous pericarditis is questioned. The pericarditis is probably always secondary to some other tuberculous lesion. Most instances of tuberculosis of the pericardium are due to a retrograde extension of the infection through the lymphatic channels from a mediastinal focus. In place of the term clinically primary tuberculous pericarditis, it is suggested that cases of tuberculous pericarditis be divided into (1) those in which the pericarditis was the most important factor in the production of the clinical picture and (2) those which occur during the course of a disseminated tuberculosis.

Tuberculosis of the pericardium occurs most often in males over 40 years of age. The colored race appears to be more susceptible to the disease than the white race. The proof of the tuberculous nature of a pericardial effusion may be extremely difficult to obtain. Inoculation of a guinea pig is often necessary. The prognosis of tuberculous pericarditis is bad. The mortality in two series reported in the literature is given as 83 per cent in both instances. Present methods of treatment of tuberculous pericarditis are unsatisfactory. In the healed state tuberculous pericarditis presents the histologic picture of a nonspecific fibrous pericarditis. Pick's disease has often been found to follow tuberculous pericarditis. Polyserositis is probably tuberculous in origin and is a condition associated with a high degree of immunity to the infection. Tuberculosis of the myocardium, endocardium, and blood vessels is rare. It is difficult to determine any exact relationship between pulmonary tuberculosis and diseases of the heart.

AUTHOR.

Koons, R. A., and Kissane, R. W.: The Incidence of Heart Disease in Children With Congenital Syphilis. Urol. & Cutan. Rev. **44**: 673, 1940.

The relative incidence of heart disease in congenitally syphilitic children closely approximates the incidence of congenital syphilis in known cardiac children.

The incidence of heart disease in congenitally syphilitic children is too small to permit consideration of syphilis as an etiological factor in the production of congenital heart disease.

The association of rheumatic heart disease and congenital heart disease is incidental.

Congenital syphilis can practically be disregarded as the etiological factor in any type of heart disease in children.

AUTHORS.

Friedman, M., Sugarman, H., and Selzer, A.: The Relationship of Renal Blood Pressure and Blood Flow to the Production of Experimental Hypertension. Am. J. Physiol. **134**: 493, 1941.

The renal hemodynamics and systemic blood pressure were studied following aortic constriction above and between the renal artery aortic orfices.

It was found that renal ischemia is not necessary for the initiation or maintenance of a chronic (renal) experimental hypertension.

AUTHORS.

Leary, T.: The Genesis of Atherosclerosis. Arch. Path. **32**: 507, 1941.

From the evidence accumulated and presented, the author points out that atherosclerosis in man and in the experimental rabbit is due to the presence of excess cholesterol esters within phagocytic cells, which first appear in the intima of the arterial wall. The cholesterol is esterified in the liver as directly observed in the experimental rabbit. The cholesterol when fed in excess to rabbits is deposited in the form of esters in the cells of the liver and adrenals. The esters as they accumulate in excess become a burden and are removed from these organs by Kupffer cells in the liver and their analogues in the adrenals. The cholesterol esters are engulfed as particulate matter by these cells. These cells, now lipoid cells, escape from the liver and adrenals through the blood and lymph systems and may produce obstruction in the lymph sinuses. The lipoid cells, having entered the blood stream, pass through the lung filter and selectively invade the arterial intima. This invasion is favored by stresses but is apparently dependent on a positive chemotaxis of the arterial wall for cells carrying cholesterol esters. The latent period after the beginning of cholesterol feeding in the rabbit and before aortic lesions appear is dependent on the production of esters in excess and their transport, as indicated in paragraphs 2 and 7 inclusive. The lipoid cells possess the power to split cholesterol esters and bring the substance into solution in an excess of fatty acids. The excess cholesterol esters are akin to silica in their irritant character. Both are difficult of metabolism, tend to stay long in tissues and stimulate a growth of connective tissue. The intravenous silica and cholesterol esters, practically alone among particulate matters, tend to cause in rabbits cirrhosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of chronic "interstitial" nephritis. The human atheroclerosis is associated with intermittent accretions of excess cholesterol esters in contrast to the continuous accretions in the rabbit fed cholesterol. That the differences in the appearance of atherosclerotic lesions in the two species are due in great part to differences in the manner of feeding. Diffuse lipoidosis is more common in the experimental rabbit, partly for the same reason.

The accepted criteria for the establishment of a causal relation between a given agent and a disease are embodied in Koch's laws. Since animals are not susceptible to all human infections, or because evident parasites cannot be cultivated, or for other reasons, various compromises have been made with these postulates. However, the evidence of a casual relation is most complete when Koch's laws can be satisfied.

In the causation of atheroclerosis the principles of Koch's laws can be fulfilled. Excess cholesterol is always present in the active stages of human atherosclerosis. It can be identified in the lesions as definitely as can the bacterial or other parasitic agents producing infections. It can be extracted from the lesions. Human arterial lesions can be reproduced experimentally by its use with more exactness than the lesions of many human infections can be reproduced by the introduction into susceptible animals of their recognized causal agents. It can be identified in and extracted from the experimental lesions.

Stresses determine the localization of lesions and influence the degree of the sclerotic processes. The efficiency of cholesterol metabolism is modified by sex and thyroid factors. Age (time plus thyroid deterioration) and heredity are also contributing elements.

AUTHOR.

Schleicher, I.: The Story of the Coronary Arteries. Anatomy, Pathology, Physiology, and Functional Pathology. Arch. f. Kreislaufforsch. **8**: 17, 1941.

This is an historical review of the coronary arteries which assembles the earlier literature on this subject adequately but neglects to some extent recent American work on the subject.

KATZ.

Feil, H., and Beck, C. S.: Coronary Sclerosis and Angina Pectoris. J. Thoracic Surg. **10**: 529, 1941.

The authors present a follow-up report on patients who had vascularized grafts placed upon the heart for the purpose of producing a collateral blood supply to the heart. Of the thirty patients operated upon, thirteen (65 per cent of those surviving) were definitely improved. Their clinical symptoms were either completely or almost entirely relieved, so that they could resume their previous occupations. Four patients (20 per cent of those surviving) were moderately improved, while in three instances (15 per cent of those surviving), there was inconsequential improvement. An anatomic study of three specimens was made. In one of these, the clinical result had been good and the specimen showed vascular anastomoses. In this group of twenty surviving patients, the high percentage of patients showing great improvement is not only significant but encouraging. This statement may be emphasized because all of these patients were seriously disabled before the operation.

AUTHORS.

Reid, L. C.: Anesthesia in Relation to Cardiac Disease. Anesthesiology **2**: 161, 1941.

All anesthetic agents and most alkaloids inhibit the enzymes, dehydrogenases, which form such an important link in the chain of events which gives rise to the production of energy by the cell. This accounts, in part at least, for the hyperglycemia during anesthesia as well as decreased carbon dioxide build-up and various degrees of failure of cellular function.

A high vitamin B content in the diet is necessary to assure an adequate supply of respiratory carriers such as flavoprotein, and nicotinic acid amide, as well as thiamin. Accordingly, the diet, preoperatively, becomes of the greatest importance to the anesthetist.

Irritation of the respiratory tract or esophagus may set up vagovagal reflexes with resulting derangement of cardiac and respiratory activity, and all such contemplated procedures, as the introduction of tubes, catheters, etc., should be covered by adequate preoperative therapy to minimize or actually prevent the undesirable reactions potentially present in autonomic reflexes.

Every operative case during the menopause which shows any cardiac symptoms or signs, or electrocardiographic findings suggestive of cardiac lesions, should have the benefit of an adequate course of estrin substitution therapy.

AUTHOR.

Lindner, E., and Katz, L. N.: Further Observations on the Action of Drugs on the Caliber of Coronary Vessels. J. Pharmacol. & Exper. Therap. **72**: 306, 1941.

The digitalis derivatives, K-strophanthin, ouabain and digifoline at times have a direct coronary constrictor action even in therapeutic doses.

Metrazol and glucose are mild, direct coronary dilators.

Calcium gluconate, in contrast with the chloride salt which is a powerful dilator of the coronary vessels, does not cause any constant or striking change in coronary caliber except that a mild dilatation occurs with large doses.

Aminophyllin and caffein sodium benzoate are consistently direct coronary dilators, the aminophyllin being the more powerful.

Papaverine hydrochloride is a powerful long-lasting direct coronary dilating agent. This and its tendency to prevent ventricular fibrillation probably explain its clinical benefits.

AUTHORS.

Riseman, J. E. F., and Linenthal, H.: The Prolonged Use of Enteric-Coated Tablets of Theobromine Sodium Acetate in the Treatment of Edema and Angina Pectoris. New England J. Med. 224: 933, 1941.

Enteric-coated tablets of theobromine sodium acetate and theophylline sodium acetate are now available, which make it possible to give therapeutically adequate doses of these drugs over long periods. By this means, the necessity of intravenous administration of diuretics may be obviated or decreased in certain patients with heart disease or nephritis, and the frequency and severity of attacks of angina pectoris may be diminished. When the drugs have been given continuously for a long time, no untoward effects have been observed except for occasional slight gastric discomfort. The optimum dosage for most patients appears to be 0.5 Gm. of enteric-coated theobromine sodium acetate, or 0.2 Gm. of enteric-coated theophylline sodium acetate, given four times daily, before meals and before retiring. Adequate dosage is necessary; in angina pectoris it is especially important to administer a dose of the medication before retiring.

AUTHORS.

Wedd, A. M., Blair, H. A., and Dwyer, G. K.: The Effect of Digoxin on the Cold Blooded Heart and Its Bearing on the Mechanism of Digitalis Action. J. Pharmacol. & Exper. Therap. 72: 394, 1941.

The effect of digoxin has been studied on spontaneously beating strips of auricle from the frog, *Rana pipiens*, and the turtle, *Pseudomys elegans*, and rhythmically driven strips of ventricle from the turtle. The spontaneous rhythm was usually slowed markedly by the drug. Measurements were made on the driven strips of the Q-T interval, the conduction time, the maximal tension, the duration of systole, the effect of a single short diastole on the ensuing Q-T, the effect of different rates on Q-T, the relation of Q-T to the duration of systole and variations of the threshold to electric stimuli. Mechanical systole is proportional to electrical systole, and both are invariably shortened by the drug. The shortening is less at higher rates of beating because the Q-T of a given tissue cannot be shortened beyond a certain limit, either by single early beats or rapid driving, and this limit is the same with or without the drug. Since the refractory period which is equal to Q-T is shortened by the drug and the threshold does not regularly change markedly, the slowing action of the drug is ascribed to the slowing of the development of excitation at the pacemaker region. Slowing of conduction usually occurred but later than Q-T changes. Tension increases were irregular and, when seen, occurred early. The amplitude of contraction may be independent of the duration of systole and the diastolic interval. The possible significance of the shortening of systole for the therapeutic action of digitalis was discussed briefly. It seems reasonable to suppose that the final action of digitalis is related to the lengthened diastole which it produces. There is reduction in the maintenance energy requirement, and longer time for recovery from contraction is given.

AUTHORS.

Cattell, M., and Gold, H.: Studies on Purified Digitalis Glucosides. III. The Relationship Between Therapeutic and Toxic Potency. J. Pharmacol. & Exper. Therap. **71:** 114, 1941.

The relative potency with regard to both therapeutic and toxic effects on isolated papillary muscles from the cat have been determined for the following glucosides: ouabain (Merck), digitoxin (Merck), digitaline (Laboratoire Nativelle), lanatoside A (Sandoz), lanatoside B (Sandoz) and lanatoside C (Cedilanid, Sandoz).

The minimum concentration of ouabain and digitoxin, i.e., that causing increased force of contraction in 50 per cent of experiments (therapeutic effect) is 1 part in 100 millions of Locke's solution; for the lanatoside compounds it is approximately 1 part in 10 millions.

When the concentration of any of the glucosides is sufficiently increased, toxic effects are produced, including extra contractions, loss of excitability, and diminished force of contraction.

The ratio of the concentrations producing therapeutic and toxic effects is the same for "digitaline nativelle" and ouabain. There is also similarity among the several lanatoside glucosides studied, and thus by this technique we have not been able to confirm the wide margin between the therapeutic and toxic dose reported by Moe and Visscher for lanatoside C.

Ouabain and "digitaline nativelle" both give a slightly higher value for the ratio of toxic to therapeutic concentration in comparison with the lanatoside compounds. The evaluation of the significance of this finding must await further evidence.

The available evidence pertaining to the questions of differences in the relationship between toxic and therapeutic doses among different glucosides is discussed, and the conclusion is reached that proof of the existence of such differences is still wanting.

AUTHORS.

Boyd, L. J., and Scherf, D.: The Electrocardiogram in Acute Emetine Intoxication. J. Pharmacol. & Exper. Therap. **71:** 362, 1941.

The alterations of the electrocardiogram after the intravenous administration of emetine hydrochloride were studied in dogs and cats.

Disturbance of intraventricular conduction is the most common change observed under these circumstances. Bradycardia and prolongation of atrioventricular conduction time develop regularly, but they are not pronounced.

If the intravenous dose does not exceed 37 mg. in dogs weighing 5 to 9 kg., the electrocardiographic alterations gradually disappear within forty-five minutes. Cardiac dilatation, especially involving the right ventricle, the development of which is simultaneous with the ventricular conduction disturbances, also vanishes within the same period.

The action of emetine is cumulative since much more pronounced effects result from the second or third injection of an equal amount of the drug although the normal electrocardiogram had been restored.

The most common arrhythmias to develop are auricular extrasystoles and auricular tachycardias. Alternation of the ventricular complexes is frequently observed during the tachycardia. Advanced stages of intoxication are required for the production of ventricular extrasystoles. Heart block with dropped beats was encountered only in cats.

AUTHORS.

Hildebrandt, F.: The Action of Strophanthin on the Blood Vessels. Arch. f. Kreislaufforsch. **8**: 137, 1941.

This is a summary of recent literature including studies published by the author. The decrease in cardiac minute output is due to constriction of the blood vessels in the skeletal muscles and gut and of the veins leaving the liver. The constriction of the renal vessels is less marked and fleeting. The cerebral vessels dilate. The coronary vessels constrict if the heart is not damaged but dilate when it is damaged and this dilatation parallels the work of the heart.

KATZ.

In Memoriam

Walter W. Hamburger

1881-1941

Walter Wile Hamburger was born in Chicago on September 10, 1881, the son of Max and Annette (Wile) Hamburger. He received his B.S. degree at the University of Chicago in 1903, his M.S. in 1904, and his M.D. degree at Rush Medical College in 1906. He served his internship at the Presbyterian Hospital, in Chicago, from 1907 to 1908. The following fourteen months (1908-1909) Dr. Hamburger did postgraduate study in pathology and internal medicine in Berlin, Munich, and Vienna, including the clinic of Friedrich Kraus at the Charity Hospital, Berlin, and the clinic of Friedrich Mueller, in Munich. He was assistant to the late Dr. Frank Billings for three years, and then began the private practice of medicine, specializing in internal medicine.

Dr. Hamburger was Assistant Clinical Professor in Medicine at Rush Medical College from 1914 to 1934, and was Clinical Professor of Medicine at the University of Chicago from 1934 to the time of his death. He was a member of the Staff of Cook County Hospital from 1913 to 1926. He was Attending Physician at Michael Reese Hospital from 1912 to 1925, and then became Senior Attending Physician. He was Chief of Staff of Michael Reese Hospital during the years 1928 and 1929. He was a Major in the Medical Corps, United States Army, from 1917 to 1919, and was Chief of the Medical Service of the Base Hospital at Camp Zachary Taylor, Louisville, Kentucky.

Dr. Hamburger, in 1915, became a Charter Member of the Institute of Medicine of Chicago and served on its Executive Committee and Board of Governors until the time of his death. He was a member of the American Society for Clinical Investigation, the Society for Experimental Biology and Medicine, the Central Society for Clinical Research, and the American Board of Internal Medicine. He was a member of the Board of Public Health Advisors of the Illinois State Department of Public Health, and was an emeritus member of the Association of American Physicians and of the Chicago Society of Internal Medicine. He belonged to the American Medical Association, the Chicago Medical Society, and the Illinois State Medical Society, and was on the Advisory Board of Psychosomatic Medicine. He was a member of Sigma Xi, Phi Beta Kappa, and Alpha Omega Alpha.

Dr. Hamburger married Edna Levis, of St. Louis, Missouri, December 27, 1911, and is survived by her and their two children, Mrs. Elizabeth H. Ries and Dr. W. W. Hamburger, Jr.

WALTER W. HAMBURGER

Dr. Hamburger played a leading role in determining the policies of the Michael Reese Hospital; his was the primary responsibility for the conception, establishment, and growth of its Cardiovascular Department, and he gave this project constant and unqualified support, though quietly keeping in the background. He was associated with many other cardiac activities in his community. He was formerly Vice-President and later a member of the Board of Governors and the Executive Committee of the Chicago Heart Association. He was a member of the Medical Advisory Board of the Sunset Camp for Convalescent Cardiac Children.

His interest in heart disease was evident in his publications. He contributed over 100 articles on internal medicine to medical journals, with particular reference to the heart and circulation. He was the author of a chapter on "Cardiac Arrhythmias" in Cecil's *Textbook of Medicine*, and of the chapter on "Gastro-Intestinal Manifestations of Cardiovascular Disease" in Portis' *Diseases of the Digestive System*. Dr. Hamburger was a member of the American Heart Association, in which he held the office of Treasurer, and was a member of the Executive Com-

mittee for many years; until 1938, he served on the Advisory Editorial Board of the AMERICAN HEART JOURNAL.

The sudden and unexpected death of Dr. Walter W. Hamburger came as a shock. It deprived the medical profession of an outstanding practitioner who was devoted to his patients, a courageous supporter of advances in medicine and public health, a scholar who placed on record many contributions which are notable for their modesty and scientific spirit. His absence will be noticed particularly in the field of cardiology, to the advancement of which he contributed greatly and in many ways.

The loss of Dr. Hamburger seems irreparable, but those of us who were his friends console ourselves that the spirit of this gentle, lovable, and scholarly man will live on.

LOUIS N. KATZ.

KAREL FREDERIK WENCKEBACH

1864-1940

A short time ago news arrived from Vienna, rather belatedly, that Karel Frederik Wenckebach had died last winter at the age of 76. A great physician, a distinguished scientist, a stimulating teacher, a cultured scholar had passed away.

The imperishable memorial built upon the scientific studies of Wenckebach constitutes an eloquent testimonial of the lasting imprint which he stamped upon medicine. Since his scientific achievements are known to every reader of this journal, an attempt to evaluate the significance of his contributions to cardiology would be superfluous. It seems more fitting in these lines, devoted to a commemoration of Wenckebach, to describe briefly some features of his development and to delineate some traits of his personality.

Born in The Hague, Wenckebach studied medicine at Utrecht, where he became engaged in the study of embryology and hematology. The discovery that he was color-blind necessitated a change in his life plan. He turned to physiology, and spent many hours in the laboratory of Engelmann, who, at this time, was employing "the method of extrasystole" in studies of the fundamental properties of the heart. The opportunity to observe these frog experiments proved decisive in Wenckebach's further development.

Subsequently, economic circumstances compelled him to leave the University and enter practice in a small Dutch village. Wenckebach often referred to this period with great satisfaction, and emphasized the diversity of problems which a country practitioner encounters and the difficulties under which they must be solved. Among his daily duties was supervision of the medical care in a home for the aged. This was extremely fortunate, for many of the charges had disturbances of cardiac rhythm. One day, while auscultating a patient, Wenckebach found a

strange arrhythmia which reminded him of the irregular movements of the lever he had seen so frequently in Engelmann's laboratory. Wenckebach loved to relate how the patient had told others in the ward that "the doctor had fallen asleep on my chest," for Wenckebach had listened for an unusually long time to that heart. An analysis of sphygmograms recorded on this and other patients permitted Wenckebach to describe extrasystoles for the first time in man (1898). His discovery of periodic dropped beats, often called Wenckebach's periods, followed soon thereafter. Their recognition by an analysis of sphygmograms is likewise a remarkable achievement when one recalls the crude apparatus then available. This work was followed by a study of pulsus alternans, and, in 1903, the first complete description of his research appeared in the form of a monograph.

KAREL FREDERIK WENCKEBACH

Two years earlier Wenckebach had given up his practice to accept a position at the University of Groningen, in Northern Holland, where he was entrusted with the direction of the medical division.

During the succeeding years his scientific development was profoundly influenced by the friendship of Sir James Mackenzie and Sir Arthur Keith. For example, by means of venous pulse tracings, registered with the Mackenzie technique, he discovered the first cases of dropped beat when conduction time remained fixed (1906). The Keith influence is

reflected in his work during the next four years, which were devoted to important investigations of the interrelation between circulation and respiration and to his classical study of pericarditis with effusion and adhesive pericarditis.

In 1911, Wenckebach was appointed Head of the Department of Medicine at the University of Strassburg, and, in 1914, he accepted the responsibility for the First Medical University Clinic in Vienna. He remained in this post until his voluntary retirement from official duties, at the age of 65, in 1929.

In 1914 a completely revised edition of his famous book appeared. Actually, it was practically a new work, and more important than its predecessor. During the same year he published a report of the beneficial effect of quinine in certain arrhythmias which established the clinical basis for this and allied compounds in cardiac therapeutics. With characteristic honesty, Wenckebach acknowledged that he became aware of the effect of quinine on disturbances of stimulus formation when one of his patients made the suggestion after careful self-observation. Although the second edition of his book contained many fundamental observations on various important arrhythmias, there was only one electrocardiogram in it. This was the last important book dealing with disturbances of cardiac rhythm based exclusively upon smoked-paper tracings.

Fully aware of the importance of electrocardiography, Wenckebach decided to obtain the assistance of Winterberg in the preparation of a new edition of his book. Six years were occupied in its preparation, and the monumental volume, *The Irregular Action of the Heart,* was published in 1927, with Winterberg as coauthor.

The case histories shown to him by his pupil Aalsmeer aroused Wenckebach's interest in the circulatory disturbances encountered in beriberi. The resultant scientific expedition to the Dutch East Indies accomplished much, and the observations were published in a monograph. These observations constituted the foundation for the recognition of non-tropical beriberi as it is seen in the United States.

It will be noted that his list of publications is not long, but each represents a distinct contribution. He objected decidedly to the writing of superfluous scientific papers, which he regarded for the most part as "pseudoscientific secretion," to employ his own term.

As Professor of Internal Medicine and Head of the First Medical Clinic, he brought this institution to its high position and did much to enhance its reputation as one of the outstanding European medical centers. He was a master of physical diagnosis. This quality, combined with his deep insight into human character, his tact, and a thoroughly optimistic attitude, made him one of the best known consultants on the continent. His practice extended far beyond the borders of little post-war Austria. In his clientele were found many of the important figures who guided the destiny of their respective countries.

Presumably some of these facts influenced his attitude toward "full-time teachers," for he was accustomed to emphasize the great importance of private practice for the research worker and for those entrusted with the teaching of medical students. He believed that private practice provided a more ample opportunity to study material and a wider range of material than is available to the physician who limits his activities to hospitalized patients.

It was rather typical of Wenckebach that each new patient immediately awakened a great interest, and the subsequent therapeutic success pleased him like a new result, although he had seen it happen thousands of times. This optimism, his real joy in therapeutic accomplishment, and his unusual charm, coupled with a complete lack of affectation or ostentation, immediately impressed everyone in contact with him.

It was one of his great regrets, to which he often gave voice, that he had been unable to accept an invitation of Sir William Osler to visit the United States. In 1923, however, he was asked to deliver the Harvey Lecture in New York and the Herter Lecture in Baltimore. He utilized this opportunity to visit many of his American friends and to study many medical institutions in this country. His impressions were published in an interesting paper, "What We Can Learn From America" (Wien. klin. Wchnschr. **37**: 217, 1924). Reference may be made to one point touched upon in that paper. He recognized the rapidly increasing importance of American developments in medicine, and, in an almost prophetic manner, urged his colleagues to added scientific efforts lest medicine in Vienna lag behind and become outdistanced by American medical achievements.

Wenckebach's life was a happy one. His rise from an obscure general practitioner in an unimportant village to one of the highest medical positions in Europe was well deserved. It was his good fortune, while still in the prime of life, to become one of the most famous physicians of Europe, and to see his scientific work recognized among fellow workers, as evidenced by honorary memberships in some of the most distinguished medical societies in the world. It was fortunate that he was permitted to serve humanity so long and so fruitfully. It was also a happy circumstance that he was able to continue his activities almost to the end of his long life. Although afflicted with a disease characterized by a prolonged and painful course, the closing phase was marked by serenity and peace.

DAVID SCHERF.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

•*Executive Committee.*

INDEX TO VOLUME 22

A

Abnormality (*see* anomaly)
Abramson, D. I., and Fierst, S. M., 566
—, Katzenstein, K. H., and Ferris, E. B., Jr., 329
Acetyl-β-methylcholine, auricular fibrillation in normal intact animals after intravenous injection of, 47
chloride, injection of, auricular fibrillation following, during attack of paroxysmal auricular tachycardia or flutter, 425*
Acetylcholine, observations on production of myocardial disease with, 116
Acidosis, diabetic, peripheral circulatory failure in, and its relation to treatment, 564*
Age, process of, in animal body, significance of tensility of aorta as index of, 661
Aged (*see* old age)
Aggeler, P. M., Lucia, S. P., and Thompson, J. H., 825
Albers, D., and Bedbur, W., 841*
Allen, Edgar V., and Leary, W. V., 719
Allergy, insulin, case of, simulating coronary occlusion, 280*
Altschule, M. D., and Iglauer, A., 430*
—, —, and Davis, D., 47
American Heart Association, announcement, 140
Aminophylline, effectiveness of, in treatment of angina pectoris, 576*
Andrus, E. C., and Hill, W. H. P., 423*
Anesthesia, choice of, in operative patient with heart disease, 285*
in relation to cardiac disease, 846*
spinal, effects of, application of formulae for afferent and efferent arteriolar resistance in human kidney, 571*
Aneurysm aortic, dissecting, spinal cord ischemia in, 305
arteriosclerotic, and senile ectasia of thoracic aorta, 458
intrapericardial aortic, 569*
mycotic, ruptured aortic valve with, due to acute bacterial endocarditis, 426
of aorta, abdominal, 137*
surgical treatment of, 136*
Angina pectoris, coronary sclerosis and, 846*
objective evidence of efficacy of medicinal therapy in, 494
occurrence of electrocardiographic changes in, similar in magnitude and in kind to those produced by myocardial infarction, 64
Angina pectoris—Cont'd
treatment of edema and, prolonged use of enteric-coated tablets of theobromine sodium acetate in, 847
effectiveness of xanthine drugs (aminophylline) in, 576*
octyl nitrite in, 519
Angiotonin, "pressor" effects of renin and, cardiac factor in, 423*
Anomaly, cardiac, "corrected transposition" and persistent rudimentary "right aorta" as evidence in support of Spitzer's theory, 568*
incidence of rheumatic and congenital heart disease among school children of Louisville, Ky., 112
tetralogy of Fallot, record case of, with comments on metabolic and pathologic studies, 754
Anoxemia, induced, further observations on effects of certain xanthine compounds in cases of coronary insufficiency as indicated by response to, 252
Aorta, abdominal, aneurysm of, 137*
aneurysm of, surgical treatment of, 136
aneurysm, dissecting, of, spinal cord ischemia in, 305
coarctation of, evidence for general distribution of peripheral resistance in, 567*
tensility of, significance of, as index of aging process in animal body, 661
thoracic (aneurysms) arteriosclerotic and senile ectasia of, 458
Aortitis, syphilitic, as cause of sudden death, 277*
Arteriography, experimental, study of, 423
Arterioles, resistance, afferent and efferent, of, formulae for, in human kidney, application to effects of spinal anesthesia, 571*
Arteriosclerosis, genesis of, 845*
peripheral lumbar sympathectomy in treatment of selected cases of, 75
relation of, experimental pulmonary arterial hypertension to, 423*
Arteritis, peripheral, tuberculous, associated with tuberculous thrombophlebitis in lungs, 702
Artery, all, arising from aortic arch, occlusion of, syndrome of, 825
carotid, common, internal and external, thrombosis in, 575*

*An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

Artery—Cont'd
constriction of, and veins, effect of, induced by paredrine in lung capacity and its subdivisions, 430*
coronary, caliber of, further observations on action of drugs on, 846*
occlusion of, case of insulin allergy simulating, 280*
multiple fresh, of patient with antecedent shock, 568
of, syndrome of painful disability of shoulder and hand complicating, 1
silent or atypical, of, 841
temporary, experimental studies on effect of. II. Production of myocardial infarction, 374
operation on, 539
sclerosis, medial, of, in infancy, 132*
of, and angina pectoris, 846*
story of, anatomy, pathology, physiology, and functional pathology, 845*
sympathectomy and experimental occlusion of, 545
thrombosis of, with recovery in case of thromboangiitis obliterans, 707
tibial artery changes in comparison with those of radial and, 573*
disease, occlusive, chronic, of, femoral vein ligation for, 428*
of heart and, synopsis of, 717 (B. rev.)
dorsal metacarpal, digital, and terminal skin of hand, relative responses of, in vasoconstrictor reflexes, 574*
large, gradual occlusion of, experimental studies on, 137*
peripheral, major, prevention of ischemic gangrene following surgical operations upon, by chemical section of cervicodorsal and lumbar sympathetics, 137*
radial, tibial artery changes in comparison with those of, and coronary arteries, 573*
renal, occlusion, partial, of, unilateral kidney with, associated hypertension, 284*
renal, occlusion, partial of, unilateral angiographic study, 423
spasm of, intermittent claudication as result of, induced by walking, 719
thrombosis, multiple, case of, occurring in professional donor, 427*
tibial, changes in, in comparison with those in radial and coronary arteries, 573*
Ash, Rachel, 439
Askey, John Martin, 1
Atherosclerosis (*see* arteriosclerosis)
Atlas, Lawrence N., 75
Auricle, fibrillation of (*see* fibrillation, auricular)
Autonomic nervous system, mechanism of, heat conservation and dissipation. I. Effects of heating body; evidence for existence of capillary dilator nerves in anterior roots, 289
Aviation, consideration of effects of oxygen lack on cardiovascular system from viewpoint of, 839*
Axis deviation, characteristic electrocardiograms in left ventricular strain with and without, 279*
Ayer, G. Darrell, and Burwell, C. S., 267

B

Baehr, G., Klemperer, P., and Pollack, A. D., 842*
Baer, S., and Isard, H. J., 713*
Bain, C. W. C., 280*
—, and Wray, S., 426*
Ballistocardiography, clinical studies with, in congestive failure, on digitalis action, on changes in ballistic form, and in certain acute experiments, 712*
Barach, Alvan L., Steiner, A., Eckman, M., and Molomut, N., 13
Barber, H., and Osborn, G. R., 280*
Bayer, O., and Wasmuht, K., 841*
Bazett, H. C., Laplace, L. B., and Scott, J. C., 737, 749
Beck, Claude S., 539
—, and Feil, H., 846*
—, and Roberts, J. T., 314
—, Stanton, E. J., and Schildt, P., 529
Bedbur, W., and Albers, D., 841*
Bedford, D. E., and Lovibond, J. L., 285
Beeson, Paul B., and Levine, S. A., 401
Bellet, Samuel, and Kershbaum, A., 195
Berconsky, I., Cossio, P., and Gamba, R., 281*
Berdez, George L., Tuohy, E. L., and Boman, P. G., 305
Bernstein, Phineas, and Mann, H., 390
Bierman, W., and Lichtman, S. S., 286*
Bigger, I. A., 136*
Blackford, L. M., and Parker, F. P., 280*
Blair, H. A., Wedd, A. M., and Dwyer, G. K., 847*
Bland, E. F., and White, P. D., 281*
Blaney, Loren F., Geiger, A. J., and Druckemiller, W. H., 630
Blood flow, relationship of renal blood pressure and, to production of experimental hypertension, 844*
velocity of, correlation of, and basal metabolic rate in various metabolic disorders, 713*
gases in, physiologic action of oxygen and carbon dioxide on coronary circulation as shown by, and electrocardiographic studies, 13

Blood—Cont'd
picture of, in rheumatic fever, 342
pressure, estimation of cardiac output from, and pulse wave velocity measurements on subject with cardiovascular disease. I. Cardiovascular disease other than aortic regurgitation, 737
II. Aortic regurgitation, 747
pressure, renal, and blood flow, relationship of, to production of experimental hypertension, 844*
stroke volume, and heart size of dog, effect of cyclopropane on, 563*
venous, collapse factor in, flow of fluid through collapsible tubes, 562*
in man, 840*
responses of, to exercise, 360
vessels, action of strophanthin on, 849*
coronary, communicating, effect of abrasion of surface of heart upon, 529
intracranial, reactivity of, in aged, 427*
Blumenthal, Basil, and Reisinger, J. A., 811
Blumgart, Herrman L., Gilligan, D. R., and Schlesinger, M. J., 374
—, Schlesinger, M. J., and Zoll, P. M., 568*
Boden, Erich, 433
Bohnengel, C., 569*
Bohning, A., Katz, L. N., and Langendorf, R., 778
Boman, P. G., Tuohy, E. L., and Berdez, G. L., 305
Book Reviews:
Cardiac classics, collection of classic works on heart and circulation, with comprehensive bibliographic accounts of authors, 578
Cardiac insufficiency, 577
Clinical aspects of electrocardiogram, 287
Diagnosis and treatment of cardiovascular disease, 433
Electrocardiography for practicing physician, 433
Heart disease, volume 1, physiology, examination and functional pathology of heart, 437
Heart in pregnancy and childbearing age, 431
Hypertension and nephritis, 139
Influence of thyroid hormone on heart and circulation, 577
Management of cardiac patient, 579
Nature therapy studies in treatment of heart, electrocardiographic studies, 436
Synopsis of diseases of heart and arteries, 716
Your heart, 716
Boyd, L. J., and Scherf, D., 715*
Boyd, T. E., and Patras, M. C., 561*
Brace, D. E., Scherf, D., and Spire, L. J., 563*
Breathing, gas-mask, influence of, on circulation of men, 427*
Bronk, D. W., Pitts, R. F., and Larrabee, M. G., 562*
Brown, C. E., and Richter, I. M., 132*
Brown, Edward E., Wasson, V. P., and Weintraub, C., 342
Browning, J. S., and Clark, C. J., 570*
Bruenn, Howard G., Williams, N. E., Carr, H. A., and Levy, R. L., 252
Burch, G. E., Neumann, C., and Cohn, A. E., 276
Burchell, Howard B., and Visscher, M. B., 794
Burton, A. C., Jeffers, W. A., Montgomery, H., 572*
Burwell, C. Sidney, and Ayer, G. D., 267

C

Calcium, action of, on human electrocardiogram, 367
Cameron, D. E., and Rosen, S. R., 427*
Campbell, H. E., 715*
Capillaries, studies of, in Raynaud's disease, 573*
Carbon dioxide, action, physiologic, of oxygen and, as shown by blood gas and electrocardiographic studies, 13
Cardiac classics, collection of classic works on heart and circulation, with comprehensive bibliographic accounts of authors, 578 (B. rev.)
Cardiovascular system, consideration of effect of oxygen lack on, from viewpoint of aviation, 839*
control, hypothalamic, of, analysis of, 562*
disease of, diagnosis and treatment of, 433 (B. rev.)
estimation of cardiac output from blood pressure and pulse wave velocity measurement on subjects with. I. Cardiovascular disease other than aortic regurgitation, 737
II. Aortic regurgitation, 749
pathology of, experimental studies of. II. Pathologic lesions in organs of cats, guinea pigs, and frogs produced by digitalis poisoning, 430*
Carotid sinus syndrome, surgery in, 428*
Carr, F. B., 570*
Carr, Henry A., Williams, N. E., Bruenn, H. G., and Levy, R. L., 252
Castleman, Benjamin, Ruffin, M. deG., and White, P. D., 458
—, Talbott, J. H., Coombs, F. S., Chamberlain, F. L., Consolazio, W. V., and White, P. D., 734
Cattell, M., and Gold, H., 848*
Chagas' disease (*see* trypanosomiasis)

Chamberlain, Francis L., Talbott, J. H., Coombs, F. S., Castleman, B., Consolazio, W. V., and White, P. D., 754
Childbearing age, heart in pregnancy and, 431 (B. rev.)
Childhood, rheumatic infection in, influence of type of onset and calendar year of onset, 439
Children, character of congestive failure in, with active rheumatic fever, 283*
incidence of heart disease in, with congenital syphilis, 844*
rheumatic, epidemic of influenza B occurring in group of, concurrent with outbreak of streptococcal pharyngitis, 282*
observation on effect of streptococcal upper respiratory infections in, 282*
school, incidence of rheumatic and congenital heart disease among, of Louisville, Ky., 112
Ch'in, K. Y., and Huang, C. H., 690
Chorea, Sydenham's, treatment of, by fever and vitamin B therapy, 426*
Christian, H. A., 132*
Circulation, coronary, action, physiologic, of oxygen and carbon dioxide on, as shown by blood gas and electrocardiogram studies, 13
capacity of, in cardiac hypertrophy, 565*
insufficiency of, further observations on effect of certain xanthine compounds in cases of, as indicated by response to induced anoxemia, 252
observations on morphology and functions of some of components of, 564*
influence of gas-mask breathing on, of men, 427*
of thyroid hormone on heart and, 577 (B. rev.)
observations, experimental, on effect of hydrostatic forces on, 839
peripheral, failure of, in diabetic acidosis and its relations to treatment, 564*
failure of mechanisms of, 714*
problems of, 575*
renal, capacity of, in hypertension, 565*
resistance, peripheral, of, evidence for general distribution of, in coarctation of aorta, 567*
time, arm to lung, of, comparative value of ether and paraldehyde as agents for measurements of, in fifty patients with and fifty patients without heart failure, 284*
venous, in lower extremities during pregnancy, 427*
Clark, C. J., and Browning, J. S., 570*
Clarke, Norman E., 367
Clarke, William O., and Hallock, P., 410
Claudication, intermittent, as result of arterial spasm induced by walking, 719
Clawson, B. J., 607
Coarctation of aorta, evidence for general distribution of peripheral resistance in, 567*
Cohen, Louis, Gray, I., Nash, P. T., and Fink, H., 425*
—, Lalich, J., and Walker, G., 105
Cohn, A. E., Neumann, C., and Burch, G. E., 276*
Cohn, C., Schecter, A. E., and Wiesel, B. H., 564*
Collapse, factor of, in measurement of venous pressure, flow of fluid through collapsible tubes, 562*
Complex, QRS, duration of, measurement of, errors in, and P-R (P-Q) interval in electrocardiogram, 321
prolongation of, further observations on mechanisms of production of short P-R interval in association with, 450
significance of low voltage of, in precordial leads, 195
R, formation of, of electrocardiogram, 567*
ventricular, variable, in heart block, and their relation to bilateral bundle branch block, 280*
Consolazio, W. V., Talbott, J. H., Coombs, F. S., Castleman, B., Chamberlain, F. L., and White, P. D., 754*
Cooke, W. T., and White, P. D., 425*
Coombs, Frederick S., Talbott, J. H., Castleman, B., Chamberlain, F. L., Consolazio, W. V., and White, P. D., 754*
Cor pulmonale (*see* heart, hypertrophy)
Corbit, J. D., Jr., 283*
—, Fouts, P. J., and Page, I. H., 714*
Corcoran, A. C., and Page, I. H., 132*, 571*
—, Smith, H. W., and Page, I. H., 571*
Correspondence, 581
Corrigendum, 275
Cos, A. J., Jr., and Dock, W., 565*
Cossio, P., Berconsky, I., and Gamba, R., 281*
Crouch, J. H., 574*
Croxatto, R., Garreton-Silva, A., Fuenzalida, O., and Viveros, R., 284*
Cushing, Edward H., and Liebow, I. M., 125
Cyclopropane, effect of, on blood pressure, stroke volume, and heart size of dog, 563*

D

Da Costa's syndrome (*see* effort syndrome)
Dally, J. F. H., 564*

Davis, David, Iglauer, A., and Altschule, M. D., 47
Death, physiologic, instantaneous, 278*
sudden, symposium on, 277*, 278*
syphilitic aortitis as cause of, 277*
Denenholz, E., and Rambar, A. C., 426*
Depropanex (*see* pancreas, extract of)
Deutsch, F., Ehrentheil, O., and Peirson, O., 573*
Diabetes, acidosis of, treatment of, peripheral circulatory failure in, and its relation to, 564*
Digitalis and normal work electrocardiogram, 683
glucosides, purified, of, studies on. III. Relationship between therapeutic and toxic potency, 848*
poisoning by, pathologic lesions in organs of cats, guinea pigs, and frogs produced by, 430*
study, electrocardiographic, quantitative, of, 230
use of, to prevent exaggerated acceleration of heart during physical exercise in patients with auricular fibrillation, 430*
Digoxin, effect of, on cold blooded heart and its bearing on mechanism of digitalis action, 847*
Diodrast, removal of, from blood by dog's explanted kidney, 571*
Diphtheria, myocardial necrosis in, 690
Diuretics, mercurial, comparison of, used in heart failure, 428*
Dock, W., 565*
—, and Cos, A. J., Jr., 565*
Dressler, M., and Moskowitz, S. N., 566*
Druckemiller, William H., Geiger, A. J., and Blaney, L. F., 230
Drugs, action of, further observations on, on caliber of coronary vessels, 846*
Dungern, M., 841*
Duryee, A. Wilbur, Schwartz, M. S., Fisher, M. M., and Wright, I. S., 122
Dwyer, C. K., Wedd, A. M., and Blair, H. A., 847*

E

Eckman, Morris, Barach, A. L., Steiner, A., and Molomut, N., 13
Eckstein, R. W., Roberts, J. T., Gregg, D. E., and Wearn, J. T., 276*
Ectasia, senile, aneurysms, arteriosclerotic, and, of thoracic aorta, 458
Edema, treatment of, and angina pectoris, prolonged use of enteric-coated tablets of theobromine sodium acetate in, 847*
Effort syndrome, 286*
Ehrentheil, O., Deutsch, F., and Peirson, O., 573*
Electrocardiogram, action, physiologic, of oxygen and carbon dioxide on coronary circulation as shown by blood gas and, 13
Electrocardiogram—Cont'd
alterations in, duration of isometric contraction, ejection time, systole, and Q-T interval, 841*
aspects, clinical, of, 287 (B. rev.)
changes following intravenous administration of magnesium sulfate. III. Combined effect with digitalis, 429*
in occurrence of, in angina pectoris similar in magnitude and in kind to those produced by myocardial infarction, 64
in rhythm of heart during resection of pericardium in chronic constrictive pericarditis, 169
of chest-leads of, due to damage to heart's surface, 425*
characteristic, in left ventricular strain with and without axis deviation, 279*
comparison of Leads IV R and IV F, 125
distribution of surface potential in chest intraventricular block, 778
duration of Q-T interval in absolute arrhythmia, 841*
in cases of massive pericardial effusion, 35
errors in, measurement of P-R (P-Q) interval and QRS duration in, 321
esophageal, normal and abnormal, with particular reference to myocardial infarction, 469
formation of R complex of, 567*
human action of calcium in, 367
in acute emetine intoxication, 715*
in experimental Chagas' disease, 567*
in induced fever, 804
nature of Leads I and II, 567
normal, 625
pattern of, effect of diffuse pericarditis on, of recent myocardial infarction, 86
significance of low voltage of QRS complex in precordial leads as compared with limb leads, 195
S-T depression, as sign of anaerobic cardiac metabolism, 841*
studies by, analysis of initiation of fibrillation, 713*
variations of, frequency of, in normal unanesthetized dogs, 105
ventricular, physiological variations in duration of, 841*
work, normal, digitalis and, 683
Electrocardiography, fetal, 390
and stethography, 840*
for practicing physician, 433 (B. rev.)
Elkin, D. C., 137*
Embolism, fat, clinical and experimental study, 424*
Emetine, intoxication, acute, by electrocardiogram in, 715*

Endocarditis, bacterial, acute, ruptured aortic valve with mycotic aneurysm due to, 426*
subacute, treatment of, 286*
subacute *Streptococcus viridans*, earlier diagnosis of, 132*
Estrogen, action, dermovascular, of, 575*
Ether, value, comparative, of, and paraldehyde as agents for measurements of arm to lung circulation time in fifty patients with and fifty without heart failure, 284*
Evans, W., and Paxon, T., 428*
Exercise, peripheral vascular response to, in hyperthyroid state, 566*
physical, use of digitalis to prevent exaggerated acceleration of heart during, in patients with auricular fibrillation, 430*
venous pressure responses to, 360
Eyster, J. A. E., and Meek, W. J., 839*

F

Farmer, L., Wechsler, H. F., and Urban, J. A., 280*
Fatherree, T. J., and Hurst, C., 180
Feil, Harold, and Beck, C. S., 846*
—, and Liebow, I. M., 683
Feldt, R. H., and Wenstrand, D. E. W., 424*
Ferris, Eugene B., Jr., Abramson, D. I., and Katzenstein, K. H., 329
Fetus, electrocardiogram in, 390
Fever, induced, electrocardiogram in, 804
Fibrillation, auricular, following injection of acetyl-β-methylcholine chloride (mecholyl) during attack of paroxysmal auricular tachycardia or flutter, 425*
in normal intact animals after intravenous injection of mecholyl, 47
use of digitalis to prevent exaggerated acceleration of heart during physical exercise in patients with, 430*
variable interval between electric and acoustic phenomena in, 245
duration of Q-T interval in, 841*
initiation of, analysis of, by electrographic studies, 713*
ventricular, ineffectiveness of vagal stimulation on, in dogs, 276*
Fierst, S. M., and Abramson, D. I., 566*
Fink, H., Cohen, L., Gray, I., and Nash, P. I., 425*
Fishberg, Arthur M., 139
Fisher, Martin M., Schwartz, M. S., Wright, I. S., and Duryee, A. W., 122
Fistula, arteriovenous, clinical and experimental observations on, 135*
Flaxman, N., 279*
Foote, Stephen A., White, P. D., and Leach, C. E., 321
Foreign body, bullet, in heart for twenty-three years, 575*
needle, hollow, passage of, into venous blood stream to heart through cardiac wall and into thorax, 835
-gas method, estimation by, of net cardiac output in conditions where there is recirculation through lungs, 561*
Fouts, P. J., Corcoran, A. C., and Page, I. H., 714*
Freedberg, A. Stone, Riseman, J. E. F., and Spiegl, E. D., 494, 519
Frey, J., 839
Friedman, B., Jarman, J., and Klemperer, P., 572*
Friedman, M., Sugarman, H., and Selzer, A., 844*
Fuenzalida, O., Garreton-Silva, A., Croxatto, R., and Viveros, R., 284*
Fujiwara, T. F., Karsner, H. T., and Simon, M. A., 423*

G

Gage, M., and Ochsner, A., 137*
Galdston, M., Govons, S., Wortis, S. B., Steele, J. M., and Taylor, H. K., 572*
Gamba, R., Cossio, P., and Berconsky, I., 281*
Gangrene, ischemic, prevention of, following surgical operations upon major peripheral arteries by chemical section of cervicodorsal and lumbar sympathetics, 137*
Garreton-Silva, A., Croxatto, R., Fuenzalida, O., and Viveros, R., 284*
Garvin, Curtis F., and Scott, R. W., 56
Geiger, Arthur J., Blaney, L. F., and Druckemiller, W. H., 230
Gilligan, D. Rourke, Blumgart, H. L., and Schlesinger, M. J., 374
Glaser, S. T., and Lesser, A., 428*
Glomerulonephritis, acute, mode of action of magnesium sulphate in reducing hypertension of, 576*
Glomus tumors, clinical picture and physiology, 574*
multiple, four in one finger tip, 574*
Gold, H., and Cattell, M., 848*
—, Modell, W., and Rothendler, H. H., 430*
Gorenberg, H., and McCleary, J., 842*
Gouley, Benjamin A., 208
Govons, S., Galdston, M., Wortis, S. B., Steele, J. M., and Taylor, H. K., 572*
Gray, Howard K., and Skinner, I. C., 428*
Gray, I., Cohen, L., Nash, P. I., and Fink, H., 425*
Graybiel, A., 839*
—, and White, P. D., 561*

Greenfield, Irving, 707
Gregg, D. E., Eckstein, R. W., Roberts, J. T., and Wearn, J. T., 276*
Gross, F., and Matthes, K., 840*
Growth, alterations in heart accompanying, and hypertrophy, 564*

H

Hahn, P., 568*
Hallock, Phillip, and Clarke, W. O., 410
Hamburger, Walter W., in memoriam, 850
Hamilton, Burton E., and Thomson, K., 431
Hannesson, H., 843*
Harris, A. S., Moe, G. K., and Wiggers, C. J., 713*
Heart, acceleration, exaggerated, use of digitalis to prevent, during physical exercise in patients with auricular fibrillation, 430*
alterations in, accompanying growth and hypertrophy, 564*
anoxemia of, S-T depression as sign of, 841*
arrhythmia, absolute, of (*see* fibrillation, auricular)
beat, idioventricular, of, comparison of vulnerable periods and fibrillation thresholds of, 277*
block, auriculo-ventricular, complete, intermittent, three observations on, 425*
with Stokes-Adams' syndrome in patient with syphilitic heart disease and diffuse myocarditis, 569*
bundle branch, bilateral, variable ventricular complexes in heart block and their relations to, 280*
pulmonary stenosis with, 280*
intraventricular, distribution of surface potential in chest, 778
ventricular complexes, variable, in, and their relation to bilateral bundle branch block, 280*
bullet in, for twenty-three years, 575*
compression, chronic, of, effect of, on size of heart muscle fibers, 314
contraction, fractionate, sequence of, at different surface regions on right auricle and ventricles of dog's heart, 839*
disease of, anesthesia in relation to, 846*
choice of anesthesia in operative patients with, 285*
congenital, incidence of rheumatic and, among school children of Louisville, Ky., 112
geographical distribution of, incidence of rheumatic and congenital heart disease among school children of Louisville, Ky., 112
in pregnancy, 570*
Heart, disease of—Cont'd
incidence of, in children with congenital syphilitis, 844*
of types of, among 30,265 autopsies, with special reference to age and sex, 607
physiology, examination and functional pathology of heart (vol. I), 437 (B. rev.)
review of significant contributions made during 1940, 561*
rheumatic, in Philadelphia Hospitals. IV. Influence of season and certain meteorological conditions, 133*
V. Distribution by locality of rheumatic conditions in Philadelphia, 134*
in pregnancy, 842*
incidence of, and congenital heart disease among school children in Louisville, Ky., 112
influence of tonsillectomy on progress of, 133*
synopsis of, and arteries, 716 (B. rev.)
syphilitic, of, auriculo-ventricular heart block with Stokes-Adams' syndrome in patient with, and diffuse myocarditis, 569*
factor of, in "pressor" effects of renin and angiotonin, 423*
failure of, comparative value of ether and paraldehyde as agents for measurement of arm to lung circulation time in fifty patients with and fifty patients without, 284*
comparison of, mercurial diuretics used in, 428*
congestive, character of, in children with active rheumatic fever, 283*
of, studies on. I. Importance of restriction of salt as compared with water, 141
hydrothorax in, 285*
myocardial degeneration with hypertrophy and, of unknown cause, 811
production and study of, in thiamin-deficient dogs, 154
filling and rate of, effect of respiration on, 712*
hypertrophy of, alterations in heart accompanying growth and, 564*
capacity of coronary bed in, 565*
myocardial degeneration, and failure of unknown cause, 811
observations in fifty autopsy cases, 56
in pregnancy and childbearing age, 431 (B. rev.)
influence of thyroid hormone on, and circulation, 577 (B. rev.)
insufficiency of, 577 (B. rev.)

Heart—Cont'd
mammalian, beating, changes in form of, as demonstrated by high-speed photography, 794
surviving, energetics of, effect of varying resistance-load and input-load on, 712*
murmur, Austin Flint, of, aortic valvular lesions associated with, 208
muscle of (*see* myocardium)
output of, estimation of, from blood pressure and pulse wave velocity measurements on subject with cardiovascular disease. I. Cardiovascular disease other than aortic regurgitation, 737
II. Aortic regurgitation, 749
output of, net (systemic) of, estimation by foreign-gas method of, in conditions where there is re-circulation through lungs, 561*
rhythm of, changes in, during resection of pericardium in chronic constrictive pericarditis as recorded electrocardiographically, 169
gallop, systolic, of, 726
nodal, atrioventricular, of, 279*
rupture, spontaneous, of, 569*
reflections on mechanism of, 568*
sarcoma, primary, of, 556
size of, effect of cyclopropane on blood pressure, stroke volume and, of dog, 563*
stroke volume of, effect of cyclopropane on blood pressure, and heart size of dog, 563*
surface of, abrasion of, effect of, upon intercoronary communications, 529
damage of, changes of chest-leads of electrocardiogram due to, 425*
tuberculosis of pericardium and, 843*
your, 716 (B. rev.)
Heat, body, conservation and dissipation of, autonomic mechanism of. I. Effect of heating body, evidence for existence of capillary dilator nerves in anterior roots, 289
Hedley, O. F., 133,* 134*
Heinbecker, Peter, 138*
Herrington, L. P., and Nelbach, J. H., 661
Herrmann, George R., 716
Herrmann, Louis G., and Neel, W., 702
Hertzman, A. B., 574*
Hildebrandt, F., 849*
Hill, W. H. P., and Andrus, E. C., 423*
Hines, E. A., Jr., and Lander, H. H., 135*
Hinohara, Shigeaki, 726
Hochrein, Max, 437
von Hofer, H., 427*
Hoff, H. E., Nahum, L. H., and Kaufman, W., 567*
Holman, Emile, 135*
Holt, J. P., 562*
Horneff, J. A., and Sappington, S. W., 573*
Horswell, Richard G., 116
Huang, C. H., and Ch'in, K. Y., 690
Hubbard, J. P., 282*
Hueper, W. C., and Ichniowski, C. T., 430*
Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C., 574*
Hurst, Cecil, and Fatherree, T. J., 180
Hussey, H. H., and Katz, S., 284*
—, and Veal, J. R., 427*
Hydrothorax in heart failure, 285*
Hyndman, Olan R., and Wolkin, J., 289
Hyperemia, reaction, observations on, on various portions of extremities, 329
Hypertension and nephritis, 139 (B. rev.)
and pressor activity of heated extracts of human kidneys, 426*
arterial, correlation of clinical and experimental observations, 132*
experimental investigation of pressor substances with blood of patients with, 284*
pulmonary, experimental, relation of, to arteriosclerosis, 423*
association of, with organic renal disease, 570*
capacity of renal vascular bed in, 565*
essential, role for surgeon in problem of, 138*
studies on. II. Association of hypertension with organic renal disease, 570*
experimental and clinical aspects of, 571*
effect of pregnancy upon, in rabbit, 283*
production of, relationship of renal blood pressure and blood flow to, 844*
factors contributing to development of, in patients suffering from renal disease, 135*
kidney, unilateral, with partial occlusion of renal artery associated with, 284*
of acute glomerulonephritis, mode of action of magnesium sulphate in reducing, 576*
sustained, following experimental unilateral renal injuries, effects of nephrectomy, 572*
Hyperthyroidism, peripheral vascular response to exercise in, 566*
Hypotension, orthostatic, types of, and their treatment, 572*

I

Ichniowski, C. T., and Hueper, W. C., 430*

Iglauer, Arnold, and Altschule, M. D., 430*
—, Davis, D., and Altschule, M. D., 47
Infancy, medical coronary sclerosis in, 132*
Infant, newborn, rheumatic fever in, 426*
young, paroxysmal tachycardia and its treatment in, 282*
Influenza B, epidemic of, occurring in group of rheumatic children concurrent with outbreak of streptococcal pharyngitis, 282*
Input-load, effect of varying resistance-load and, on energetics of surviving mammalian heart, 712*
Insulin, allergy to, case of, simulating coronary occlusion, 280*
Isard, H. J., and Baer, S., 713*

J

Jarman, J., Friedman, B., and Klemperer, P., 572*
Jason, R. S., 569*
Jean, Nicholas Corvisart, life and times of, 564*
Jeffers, W. A., Montgomery, H., and Burton, A. C., 572*
Jochim, K., Katz, L. N., Lindner, E., and Landowne, M., 712*
Johnson, C. A., 284*
Johnston, Franklin D., and Wilson, F. N., 64
Jones, Benjamin C., Jr., and Weir, D. R., 556

K

Kaplan, L. G., and Katz, L. N., 279*
Karsner, H. T., Simon, M. A., and Fujiwara, T. F., 423*
Katz, L. N., Bohning, A., and Langendorf, R., 778
—, Jochim, K., Lindner, E., and Landowne, M., 712*
—, and Kaplan, L. G., 279*
—, and Lindner, E., 846*
Katz, S., and Hussey, H. H., 284*
Katzenstein, Kurt H., Abramson, D. I., and Ferris, E. B., Jr., 329
Kaufman, W., Hoff, H. E., and Nahum, L. H., 567*
Kershbaum, Alfred, and Bellet, S., 195
Keys, A., 561*
Keys, Thomas E., and Willius, F. A., 578
Kidney, disease of, factors contributing to development of hypertension in patients suffering from, 135*
organic, association of hypertension with, 570*
formulae for afferent and efferent arteriolar resistance in, application to effects of spinal anesthesia, 571*
injury, experimental, unilateral, of sustained hypertension following effect of nephrectomy, 572*
Kidney, injury—Cont'd
explanted, dog's, removal of diodrast from blood by, 571*
unilateral, with partial occlusion of renal artery associated with hypertension, 284*
Kienle, Franz, 436
Kisch, B., 425*
Kissane, R. W., and Koons, R. A., 844*
Klemperer, P., Friedman, B., and Jarman, J., 572*
—, Pollack, A. D., and Baehr, G., 842*
Knies, Phillip T., 804
Koons, R. A., and Kissane, R. W., 844*
Kruger, Erich, McGovern, T., and Wright, I. S., 583
Krumwiede, E., and Kuttner, A. G., 282*
Kuttner, A. G., and Krumwiede, E., 282*
—, Reyersbach, G., and Lenert, T. F., 282*

L

Lalicch, Joseph, Cohen, L., and Walker, G., 105
Lamport, H., 571*
Lander, H. H., and Hines, E. A., Jr., 135*
Landis, E. M., 426*
Landowne, M., Katz, L. N., Jochim, K., and Lindner, E., 712*
Langendorf, R., 86
—, Bohning, A., and Katz, L. N., 778
Laplace, L. B., Bazett, H. C., and Scott, J. C., 737, 749
Larrabee, M. G., Pitts, R. F., and Bronk, D. W., 562*
Larsen, Kaj, and Skúlason, Th., 625, 645
Laufer, S. T., 842*
Leach, C. Edward, White, P. D., and Foote, S. A., 321
Leads, chest, changes of, of electrocardiogram due to damage of heart's surface, 425*
IV R and IV F, comparison of, 125
precordial, significance of low voltage of QRS complex in, comparison with limb leads, 195
Leaman, William G., 579
Leary, T., 277,* 845*
Leary, Walter V., and Allen, E. V., 719
Lenert, T. F., Reyersbach, G., and Kuttner, A. G., 282*
LeRoy, G. V., 576*
Lesser, A., and Glaser, S. T., 428
Levine, Samuel A., and Beeson, P. B., 401
Levy, Robert L., Williams, N. E., Carr, H. A., and Bruenn, H. G., 252
Lichtman, S. S., and Bierman, W., 286*
Liebow, A. A., and McFarland, W., 568*
Liebow, Irving M., and Cushing, E. H., 125
—, and Feil, H., 683
Lindner, E., and Katz, L. N., 846*
—, —, Jochim, K., and Landowne, M., 712*
Linenthal, Harry, and Riseman, J. E. F., 219, 847*

Lladó, Cristián Cortés, 577
Louisville, Ky., incidence of rheumatic and congenital heart disease among school children of, 112
Lovibond, J. L., and Bedford, D. E., 285*
Lucia, S. P., Aggeler, P. M., and Thompson, J. H., 825
Luisada, Aldo, 245
Lungs, ossification, nodular of, pulmonary stenosis and, 281*
Lupus, erythematosus, disseminated, pathology of, 842*

M

Magnesium sulfate, electrocardiographic changes following intravenous administration of. III. Combined effect with digitalis, 429*
mode of action in reducing hypertension of acute glomerulonephritis, 576*
Mann, Hubert, and Bernstein, P., 390
Matthes, K., and Gross, F., 840*
McCleary, J., and Gorenberg, H., 842*
McDowall, R. J. S., 575*
McFarland, W., and Liebow, A. A., 568*
McGovern, Teresa, Wright, I. S., and Kruger, E., 583
Mecholyl (*see* acetyl-β-methylcholine)
Meek, W. J., and Eyster, J. A. E., 839*
Meiks, L. T., 133*
Metabolism, disorders, various, of, correlation of velocity of blood flow and basal metabolic rate in, 713*
rate, basal, of, correlation of velocity of blood flow and, in various metabolic disorders, 713*
Miller, J. R., and Van Dellen, T. R., 429*
Modell, W., Gold, H., and Rothendler, H. H., 430*
Moe, G. K., Harris, A. S., and Wiggers, C. S., 713*
—, Wégria, R., and Wiggers, C. J., 277*
Molomut, Norman, Barach, A. L., Steiner, A., and Eckman, M., 13
Montgomery, H., Jeffers, W. A., and Burton, A. C., 572*
Montgomery, L. C., 427*
Moritz, A. R., 278*
Moskowitz, S. N., and Dressler, M., 566*
Mulholland, John H., and Rovenstine, E. A., 428*
Myocarditis, diffuse, auriculo-ventricular heart block with Stokes-Adams' syndrome in patient with syphilitic heart disease and, 569
Myocardium, contusion of, fatal case of, 280*
degeneration of, with hypertrophy and failure of unknown cause, 811
disease of, observations on production of, with acetylcholine, 116
Myocardium—Cont'd
fibers of, size of, effect of chronic cardiac compression on, 314
infarction of, electrocardiogram, normal and abnormal esophageal with particular reference to, 469
occurrence of electrocardiographic changes in angina pectoris, similar in magnitude and in kind to those produced by, 64
production of, experimental studies on effect of temporary occlusion of coronary arteries, 374
recent, effect of diffuse pericarditis on electrocardiographic pattern of, 86
subacute, of, or necrosis, 842*
necrosis of, in diphtheria, 690

N

Nahum, L. H., Hoff, H. E., and Kaufman, W., 567*
Nash, P. I., Cohen, L., Gray, I., and Fink, H., 425*
Nature therapy studies of treatment of heart disease, 436 (B. rev.)
Neel, William, and Herrmann, L. G., 702
Nelbach, Jean Hume, and Herrington, L. P., 661
Nephritis, hypertension and, 139 (B. rev.)
nephrotoxic, observations on clinical and functional course of, in dogs, 714*
Nerves, capillary, dilator, evidence for existence of, in anterior roots, 289
vagus, stimulation of, ineffectiveness of, on ventricular fibrillation in dogs, 276*
Neumann, C., Cohn, A. E., and Burch, G. E., 276*
Nomenclature, diseases and abnormalities of blood and lymph vessels of extremities, 549
Nyboer, Jan, 469

O

Obituaries, 850, 852
Occlusion, experimental, sympathectomy and, of coronary artery, 545
Ochsner, A., and Gage, M., 137*
Octyl nitrite, in treatment of angina pectoris, 519
Old age, reactivity of intracranial vessels in, 427*
Osborn, G. R., and Barber, H., 280*
Oxygen, action, physiologic, of, and carbon dioxide, on coronary circulation as shown by blood gas and electrocardiographic studies, 13
lack of, effects of, consideration of, on cardiovascular system from viewpoint of aviation, 839*

P

Page, I. H., and Corcoran, A. C., 132,* 571*
—, —, and Smith, H. W., 571*
—, Fouts, P. S., and Corcoran, A. C., 714*
Pain, disabling, syndrome of, of shoulder and hand, complicating coronary occlusion, 1
studies on, observations on pain due to local cooling and on factors involved in "cold pressor" effect, 566*
Pancreas extract, deproteinated, effect of intravenous administration in rabbits, 122
Paraldehyde, value, comparative, of ether and, as agents for measurement of arm to lung circulation in fifty patients with and fifty patients without heart failure, 284*
Pardee, Harold E. B., 287*
Paredrine (*see* p-hydroxy-α-methylphenylethylamine hydrobromide)
Parker, F. P., and Blackford, L. M., 280*
Patient, cardiac, management of, 579 (B. rev.)
Patras, Mary C., and Boyd, T. E., 561*
Paxon, T., and Evans, W., 428*
Pearse, H. E., 137*
Peirson, O., Deutsch, F., and Ehrentheil, 573*
Pericarditis, constrictive, chronic, changes in rhythm of heart during resection of pericardium as recorded electrocardiographically, 169
pleuritis and, 267
diffuse, effect of, on electrocardiographic pattern of recent myocardial infarction, 86
leucemic, 417
Pericardium, effusion, massive, in duration of electrical systole (Q-T interval) in cases of, 35
resection, changes in rhythm of heart during, in chronic constrictive pericarditis as recorded electrocardiographically, 169
tuberculosis of, and heart, 843*
p-hydroxy-α-methylphenylethylamine hydrobromide, effect of arterial and venous constriction induced by, on lung capacity and its subdivisions, 430*
Peripheral vascular system, disease of, pernio, 583
Pernio, vascular disease, 583
Philadelphia, Hospital of, rheumatic disease in, 133,* 134*
Photography, high-speed, changes in form of beating mammalian heart as demonstrated by, 794
Pitts, R. F., Larrabee, M. G., and Bronk, D. W., 562*
Pleuritis, constrictive, and pericarditis, 267
Plewes, B., 574*
Pollack, A. D., Klemperer, P., and Baehr, G., 842*
Porter, Reno R., Swank, R. L., and Yeomans, A., 154
Posture, change of, alternations of T waves caused by, 279*
P-R interval, measurement of, errors in, and QRS duration in electrocardiogram, 321
short, further observations on mechanism of production of, in association with prolongation of QRS complex, 450
Prado, A. De A., 569*
Pregnancy, effect of, on experimental hypertension in, in rabbit, 283*
heart disease in, 570*
heart disease, rheumatic, in, 842
heart in, and childbearing age, 431 (B. rev.)
paroxysmal auricular tachycardia complicating, 570*
venous circulation in lower extremities during, 427*
Pressor activity, hypertension and, of heated extracts of human kidneys, 426*
substance, investigation, experimental, with blood of patients with arterial hypertension, 284*
Pulse wave, velocity of, estimation of cardiac output from blood pressure measurements of, on subjects with cardiovascular disease. I. Cardiovascular disease other than aortic regurgitation, 737
II. Aortic regurgitation, 749

Q

Q-T interval, duration of, in absolute arrhythmia, 841*
in cases of massive pericardial effusion, 35
Quinine dihydrochloride, treatment of paroxysmal ventricular tachycardia with, 219

R

Rambar, A. C., and Denenholz, E., 426*
Rapoport, M., and Rubin, M. I., 576*
Rasmussen, Hakon, 577
Raynaud's disease, capillary studies in, 573*
symptoms of, study of clinical manifestations and results of treatment of twenty-two patients with, 284*
Reid, L. C., 846*
Reisinger, John A., and Blumenthal, B., 811
Renin, effects, "pressor," of, and angiotonin, cardiac factor in, 423*

Resistance-load, effect of varying, and input-load on energetics of surviving mammalian heart, 712*
Respiration, effect of, on filling and rate of heart, 712*
phases of, variations in filling and output of ventricles with, 561
Reyersbach, G., Lenert, T. F., and Kuttner, A. G., 282*
Reynolds, S. R. M., 575*
Rheumatic fever, active, character of congestive failure in children with, 283*
blood picture in, 342
children with, epidemic of influenza B occurring in group of, concurrent with outbreak of streptococcal pharyngitis, 282*
in childhood, influence of type of onset and calendar year of onset, 439
in newborn infant, 426*
observations on effect of streptococcal upper respiratory infections on, 282*
Richter, I. M., and Brown, C. E., 132*
Riggs, T. F., and Satterthwaite, R. W., 284*
Riseman, Joseph E. F., Freedberg, A. S., and Spiegl, E. D., 494, 519
—, and Linenthal, H., 219, 847*
Roberts, Joseph T., and Beck, C. S., 314
—, Eckstein, R. W., Gregg, D. E., and Wearn, J. T., 276*
Robertson, T. D., Hunter, W. C., Sneeden, V. D., and Snyder, G. A. C., 574*
Rosen, S. R., and Cameron, D. E., 427*
Rovenstein, E. A., and Mulholland, J. H., 428*
Rubin, M. I., and Rapoport, M., 576*
Ruffin, Marshall deG., Castleman, B., and White, P. D., 458
Rupture, spontaneous, of heart, 569*
reflections on mechanism of, 568*

S

Salt, restriction of, importance of, as compared with water, in congestive heart failure, 141
Sappington, S. W., and Horneff, J. A., 573*
Sarcoma, primary, of heart, 556
Satterthwaite, R. W., and Riggs, T. F., 284*
Sauer, P. K., 285*
Schecter, A. E., Wiesel, B. H., and Cohn, C., 564*
Scherf, D., and Boyd, L. S., 715*
—, Brace, D. E., and Spire, L. J., 563*
—, and Weissberg, J., 279*
Schildt, Paul, Stanton, Eugene J., and Beck, C. S., 529
Schleicher, I., 845*
Schlesinger, Monroe J., Blumgart, H. L., and Gilligan, D. R., 374
—, —, and Zoll, P. M., 568*
Schroeder, Harry A., 141
—, and Steele, J. M., 570*
Schwartz, M. Stephen, Fisher, M. M., Wright, I. S., and Duryee, A. W., 122
Scott, J. C., Bazett, H. C., and Laplace, L. B., 737, 749
Scott, Roy W., and Garvin, C. F., 56
Scuderi, C. S., 423*
Selzer, A., Friedman, M., and Sugarman, H., 844*
Shapiro, Shepard, 835
Simbury, E. J., 569*
Simon, M. A., Karsner, H. T., and Fujiwara, T. F., 423*
Skin temperature, cooling, local, of, observations on pain due to, and on factors involved in "cold pressor" effect, 566*
Skinner, I. C., and Gray, H. K., 428
Skúlason, Th., and Larsen, Kaj, 625, 645
Smith, H. W., Corcoran, A. C., and Page, I. H., 571*
Sneeden, V. D., Hunter, W. C., Robertson, T. D., and Snyder, G. A. C., 574*
Snyder, G. A. C., Hunter, W. C., Sneeden, V. D., and Robertson, T. D., 574*
Spiegl, Erwin D., Freedberg, A. S., and Riseman, J. E. F., 494, 519
Spinal cord, ischemia of, in dissecting aortic aneurysm, 305
Spire, L. J., Brace, D. E., and Scherf, D., 563*
Spitzer's theory, "corrected transposition" and persistent rudimentary "right aorta" as evidence in support of, 568*
Sprague, H. B., and Walsh, B. J., 283*
Stanton, Eugene J., Schildt, P., and Beck, C. S., 529
Starr, L., 712*
Statistics, vital tool in clinical medicine, 715*
Steele, J. M., 567*
—, Galdston, M., Govons, S., Wortis, S. B., and Taylor, H. K., 572*
—, and Schroeder, H. A., 570*
Stein, Joseph M., 716
Steiner, Alfred, Barach, A. L., Eckman, M., and Molomut, N., 13
Stethography, fetal electrocardiography and, 840*
Stewart, Harold, J., and Bailey, R. L., Jr., 169
Stokes-Adams' syndrome, auriculo-ventricular heart block with, in patient with syphilitic heart disease and diffuse myocarditis, 369*
Stone, S., 426*
Streptococcus pharyngitis, epidemic of influenza B occurring in group of rheumatic children concurrent with outbreak of, 282*

Streptococcus—Cont'd
upper respiratory infections with observations on effect of, on rheumatic children, 282*
Strombeck, J. P., 423*
Strophanthin, action of, on blood vessels, 849*
Stroud, W. D., 433
—, and Wagner, J. A., 841*
Sugarman, H., Friedman, M., and Selzer, A., 844*
Surgeon, role for, in problem of essential hypertension, 138*
Swank, Roy L., Porter, R. R., and Yeomans, A., 154
Sympathectomy, and occlusion, experimental, of coronary artery, 545
chemical, prevention of ischemic gangrene following surgical operations upon major peripheral arteries by, 137*
lumbar, in treatment of selected cases of peripheral or arteriosclerotic disease, 75
Syphilitis, congenital, incidence of heart disease in children with, 844*
Szekely, P., 360

T

T waves, alterations of, caused by change of posture, 279*
Tachycardia, auricular, paroxysmal, auricular fibrillation, following injection of acetyl-β-methylcholine chloride (mecholyl) during attack of, 425*
complicating pregnancy, 570*
paroxysmal, and its treatment in young infants, 282*
ventricular, paroxysmal, favorable prognosis in absence of acute cardiac damage and its treatment with parenterally administered quinine dihydrochloride, 219
paroxysms of, Wolff-Parkinson-White syndrome with, 401
Talbott, John H., Coombs, F. S., Castleman, B., Chamberlain, F. L., Consolazio, W. V., and White, P. D., 754
Taquini, A. C., 567*
Taylor, H. K., Galdston, M., Govons, S., Wortis, S. B., and Steele, J. M., 572*
Teran, V. S., 425*
Theobromine sodium acetate, tablets, enteric-coated, prolonged use of, in treatment of edema and angina pectoris, 847*
Thiamin hydrochloride, dogs deficient in, production and study of cardiac failure in, 154
Thompson, J. H., Aggeler, P. M., and Lucia, S. P., 825
Thomson, K. Jefferson, and Hamilton, B. E., 431
Thromboangiitis obliterans, coronary artery thrombosis with recovery in, 707
spa treatment of, 180
Thrombophlebitis, tuberculous, tuberculous peripheral arteries associated with, in lungs, 702
Thyroid gland, hormone of, influence of, on heart and circulation, 577 (B. rev.)
Tonsillectomy, influence of, on progress of rheumatic heart disease, 133*
Trypanosomiasis, experimental, electrocardiogram in, 567*
Tuberculosis of pericardium and heart, 843*
Tung, Chen-Lang, 35
Tuohy, E. L., Boman, P. G., and Berdez, G. L., 305
Turner, G. G., 575*

U

Urban, J. A., Wechsler, H. F., and Farmer, L., 280*

V

Valve, aortic, insufficiency of, due to syphilis, study of its genesis, 569*
lesion of, associated with Austin Flint murmur, 208
ruptured, with mycotic aneurysm due to acute bacterial endocarditis, 426*
stenosis, calcareous, of, report of nine cases with autopsy findings, 425
mitral, stenosis of, after eighty, 281*
pulmonary, stenosis of, and nodular ossification of lungs, 281*
with bundle branch block, 280*
Van Dellen, T. R., and Miller, J. R., 429*
Vascular system, peripheral, responses of, to exercise in hyperthyroid state, 566*
Vasoconstrictor reflex, relative responses of dorsal metacarpal, digital and terminal skin arteries of hand in, 574*
Veal, J. R., and Hussey, H. H., 427*
Veins, constriction of arteries and, effect of, induced by paredrine on lung capacity and its subdivisions, 430*
deep, of leg, thrombosis of, its clinical significance as exemplified in three hundred and fifty-one autopsies, 574*
femoral, ligation of, for chronic occlusive arterial disease, 428*
pressure in (*see* blood pressure, venous)

Veins—Cont'd
pulsation, systolic, generalized, significance of, with report of case in which there was marked pulsation of varicose veins, 410
thebesian, observations on role of, and luminal vessels in right ventricle, 276*
varicose, pulsation, systolic, marked, of, significance of generalized systolic pulsation of veins, 410
Vena cava, superior, occlusion, constriction of, 428*
Venous pressure (*see* blood pressure, venous)
Ventricle, left, strain of, with and without left axis deviation, characteristic electrocardiograms in, 279*
right, observations on role of thebesian veins and luminal vessels in, 276*
variations in filling and output of, with phases of respiration, 561
Visscher, M. B., and Burchell, H. B., 794
Vitamin B therapy, treatment of Sydenham's chorea by fever, and, 426*
Viveros, R., Garreton-Silva, A., Croxatto, R., and Fuenzalida, O., 284*

W

Wagner, J. A., and Stroud, W. D., 841*
Walker, George, Lalich, J., and Cohen, L., 105
Walking, intermittent claudication as result of arterial spasm induced by, 719
Walsh, B. J., and Sprague, H. B., 283*
Wasmuht, K., and Bayer, O., 841*
Wasson, Valentina P., Brown, E. E., and Weintraub, C., 342
Water, loss of, quantitative method for measurement of rate of, from small areas, with results for finger tip, toe tip and posterosuperior portion of pinna of normal resting adults, 276*
restrictions of salt as compared with, in congestive heart failure, 141
Wearn, J. T., 564*
—, Eckstein, R. W., Roberts, J. T., and Gregg, D. E., 276
Wechsler, H. F., Farmer, L., and Urban, J. A., 280
Wedd, A. M., Blair, H. A., and Dwyer, G. K., 847*
Wégria, R., Moe, G. K., and Wiggers, C. J., 277*
Weintraub, Clarice, Wasson, V. P., and Brown, E. E., 342
Weir, David R., and Jones, B. C., Jr., 556
Weiss, Morris M., 112
Weiss, S., 278*
Weltz, G. A., 712*
Wenckebach, Karel Frederik, in memoriam, 852
Wendkos, Martin H., 417
Wendt, L., 841*
Wenstrand, D. E. W., and Feldt, R. H., 424*
White, P. D., and Bland, E. F., 281*
—, and Cooke, W. T., 425*
—, and Graybiel, A., 561*
White, Paul D., Leach, C. E., and Foote, S. A., 321
—, Ruffin, M. deG., and Castleman, B., 458
—, Talbott, J. H., Coombs, F. S., Castleman, B., Chamberlain, F. L., and Consolazio, W. V., 754
Wiesel, B. H., Schecter, A. E., and Cohn, C., 564*
Wiggers, C. J., 276*, 714*
—, Moe, G. K., and Harris, A. S., 713*
—, Wégria, R., and Moe, G. K., 277*
Williams, Norman E., Carr, H. A., Bruenn, H. G., and Levy, R. L., 252
Willius, Fredrick A., and Keys, T. E., 578
Wilson, Frank N., and Johnson, F. D., 64
Wolf, S., and Hardy, J. D., 566*
Wolferth, Charles C., and Wood, F. C., 450
Wolff-Parkinson-White syndrome, with paroxysms of ventricular tachycardia, 401
Wolkin, Julius, and Hyndman, O. R., 289
Wood, Francis C., and Wolferth, C. C., 450
Wood, P., 286*
Wortis, S. B., Galdston, M., Govons, S., Steele, J. M., and Taylor, H. K., 572*
Wray, S., and Bain, C. W. C., 426*
Wright, Irving S., Schwartz, M. S., Fisher, M. M., and Duryee, A. W., 122
—, McGovern, T., and Kruger, E., 583

X

Xanthine compounds, effects of, further observations on, in cases of coronary insufficiency as indicated by response to induced anoxemia, 252
drugs, effectiveness of, in treatment of angina pectoris. I. Aminophylline, 576*

Y

Yeomans, Andrew, Swank, R. L., and Porter, R. R., 154
Yodice, Arnaldo, 545

Z

Zoll, P. M., Blumgart, H. L., and Schlesinger, M. J., 568

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Contents on Inside Cover

The American Heart Journal

CONTENTS FOR DECEMBER, 1941

Original Communications

Intermittent Claudication as a Result of Arterial Spasm Induced by Walking. William V. Leary, M.D., and Edgar V. Allen, M.D., Rochester, Minn. ---- 719

Systolic Gallop Rhythm. Shigeaki Hinohara, M.D., Kyoto, Japan ---- 726

The Estimation of Cardiac Output From Blood Pressure and Pulse Wave Velocity Measurements on Subjects With Cardiovascular Disease.

I. Cardiovascular Disease Other Than Aortic Regurgitation. H. C. Bazett, M.D., L. B. Laplace, M.D., and J. C. Scott, Ph.D., Philadelphia, Pa. ---- 737

II. Aortic Regurgitation. H. C. Bazett, M.D., L. B. Laplace, M.D., and J. C. Scott, Ph.D., Philadelphia, Pa. ---- 749

A Record Case of the Tetralogy of Fallot, With Comments on Metabolic and Pathologic Studies. John H. Talbott, M.D., Frederick S. Coombs, M.D., Benjamin Castleman, M.D., Francis L. Chamberlain, M.D., W. V. Consolazio, B.S., and Paul D. White, M.D., Boston, Mass. ---- 754

The Distribution of Surface Potential on the Chest in Intraventricular Block. A. Bohning, M.D., L. N. Katz, M.D., and R. Langendorf, M.D., Chicago, Ill. ---- 778

The Changes in the Form of the Beating Mammalian Heart, as Demonstrated by High-Speed Photography. Howard B. Burchell, M.D., and M. B. Visscher, M.D., Minneapolis, Minn. ---- 794

The Electrocardiogram in Induced Fever. Phillip T. Knies, M.D., Columbus, Ohio ---- 804

Myocardial Degeneration With Hypertrophy and Failure of Unknown Cause. John A. Reisinger, M.D., and Basil Blumenthal, M.D., Washington, D. C. 811

A Syndrome Due to Occlusion of All Arteries Arising From the Aortic Arch. P. M. Aggeler, M.D., S. P. Lucia, M.D., and J. H. Thompson, San Francisco, Calif. ---- 825

Department of Clinical Reports

Passage of a Hollow Needle Into the Venous Blood Stream to the Heart, Through the Cardiac Wall and Into the Thorax. Shepard Shapiro, M.D., New York, N. Y. ---- 835

Department of Reviews and Abstracts

Selected Abstracts ---- 839

In Memoriam

Walter W. Hamburger ---- 850

Karel Frederik Wenckebach ---- 852

American Heart Association, Inc. ---- 856

Index

Index ---- 857

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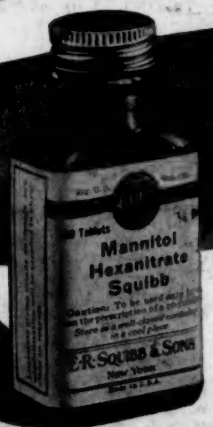

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